Practice research in the field of rheumatoid arthritis

Focus on leflunomide, parenteral gold and drug-drug interactions

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Cover photo: polarisation microscopic image of cholesterol crystals in shoulder synovial fluid from a patient with long-standing rheumatoid arthritis

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Voor Fenny
Voor mijn ouders

Contents of the thesis

Chapter 1

Scope and objectives of the thesis

Observational studies: focus on leflunomide

The view that randomized controlled trials are the ‘gold standard’ for evaluation and that observational methods have little additional value is widely accepted. According to some experts, the results of observational studies should not be used for defining evidence-based medical care. The major criticism of observational studies is that unrecognized confounding factors may influence the results [1]. However, results from a study comparing the results of observational and randomized, controlled studies in 19 different fields of medicine, suggest that observational studies usually do provide valid information [2].

One of the major reasons to conduct observational studies is the potentially limited external validity of the results of the randomized controlled trial. To what extent are the results of the trial generalisable to a population not treated in the setting of a specific trial? Three potential reasons for limited external validity can be recognized. The first may be that the health care providers in the setting of clinical trials are unrepresentative, for example because they are innovators. Secondly, the patients included in the trials may have characteristics different from the patients treated outside the setting of the trial. Thirdly, the treatment in the trial may be atypical. For example, patients included in trials may receive different care due to intensified follow-up [1]. These aspects may introduce bias in the results of the trial, resulting in limited external validity.

In the treatment of rheumatoid arthritis a number of therapeutical options are available. The potential algorithms to prescribe these medications change rapidly. New medications enter the market, medication is prescribed in combination therapy, in higher doses and earlier in the disease process. In combination with the development of practical tools for evaluating disease activity and response to treatment [3], these changing algorithms provide the rationale for studying treatment outcomes in observational studies in rheumatoid arthritis.

In the last few years, on the basis of results from large randomized controlled trials, leflunomide, the tumor-necrosis alpha antagonists and anakinra (interleukin-1 receptor antagonist) were registered for the treatment of rheumatoid arthritis (RA) [4-9]. To estimate the additional value in daily practice, critical evaluation of treatment effects in observational studies in the setting of day-to-day care, complementary to the results of randomized controlled trials, may be considered as essential.

Chapter 2 highlights aspects of the use of leflunomide for the treatment of RA in daily rheumatological practice. **Chapter 2.1** describes a long-term follow-up study of patients with RA starting leflunomide therapy in the first four years after registration. The objective is to

study the effectiveness, incidence of adverse drug reactions and withdrawal from leflunomide in an outpatient population with RA in the setting of care-as-usual. Shortly after the registration of leflunomide for the treatment of RA a number of reports of severe hepatotoxicity were published. Although in these reports, besides leflunomide exposure, other potential factors for hepatotoxicity were present, hepatotoxicity became an important safety issue concerning leflunomide. In **chapter 2.2** the incidence and severity of hepatotoxicity in terms of elevations of plasma liver enzyme activities in patients on leflunomide treatment is studied. Information on predictors for better survival of leflunomide use, at the start of leflunomide therapy may offer opportunities for treatment optimization. In **chapter 2.3** possible predictors for better leflunomide survival are studied. From the long term follow-up data of patients treated with leflunomide for RA in two regions in the Netherlands (Twente and Friesland) a set of patient-, disease- and treatment characteristics were analysed to detect potential predictors.

Therapeutic drug monitoring: focus on A77 1726, the active metabolite of leflunomide

From randomized controlled trials with leflunomide it is known that a large proportion (up to 47%) of patients withdraw leflunomide therapy due to adverse effects and inefficacy within 12 months after start of therapy [5,6]. Studies in clinical practice, outside the setting of randomized controlled trials, suggest even higher withdrawal rates [10-12]. For this reason optimization of leflunomide therapy is warranted. Therapeutic drug monitoring based on steady state serum concentrations of the active metabolite of leflunomide, A77 1726, may allow individualised dose adjustment and consequently increase clinical effectiveness. In phase II pharmacokinetic population modelling studies, a relationship between steady state A77 1726 serum concentrations < 13 mg/L and a reduced probability of clinical success is described [13]. However, information on A77 1726 serum concentrations is not incorporated in current clinical decision making in the rheumatological practice. For this reason, in **chapter 3** the potential role of therapeutic drug monitoring in leflunomide treatment optimization is studied.

In **chapter 3.1** we describe the technical and clinical validation of a high-performance liquid chromatography method with ultraviolet detection for the analyses of A77 1726. Using this validated method, in **chapter 3.2**, the relationship between RA disease activity and the

steady state serum concentrations of A77 1726 in patients treated with leflunomide is studied.

Switching therapies: focus on parenteral gold therapy

The market of rheumatoid arthritis treatment changes as new therapies are registered, and existing treatment options are withdrawn from the market. For patients using these withdrawn therapies, alternatives have to be found. A recent example is the withdrawal of aurothioglucose from the Dutch market due to insufficient quality of the raw material. Aurothiomalate was registered shortly after withdrawal of aurothioglucose and presented as the alternative preparation. Although never formally studied, some publications suggest that switching from aurothioglucose to aurothiomalate may be associated with the introduction of novel clinical problems [14,15].

To study earlier suggestions of negative safety of the aqueous aurothiomalate preparation, we monitored patients switching from the oily aurothioglucose preparation Auromyose® to the aqueous aurothiomalate preparation Tauredon® in a national case series study in the Netherlands. **Chapter 4** describes the results of the follow-up of a cohort of patients during the first year after switching from aurothioglucose to aurothiomalate.

Drug safety: focus on drug-drug interactions with disease-modifying antirheumatic drugs

When prescribing and administering drugs, drug related problems may occur. Drug related problems include medication errors (involving an error in the process of prescribing, dispensing or administering a drug, whether there are adverse consequences or not) and adverse drug reactions (any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or the modification of physiological function) [16].

The possibility of drugs to influence each others safety or efficacy is known as a drug-drug interaction (DDI). DDI may increase morbidity and mortality and may lead to hospital admission [17-19]. Due to ageing and the presence of comorbidity in the population with RA, patients are prone to polypharmacy and therefore are at risk for the adverse reactions due to DDI.

Many sources for information of DDI are available for health care providers, ranging from the summaries of product characteristics and product leaflets to text books and internet sites [20,21]. However, knowledge of a DDI between two drugs is no guarantee for timely recognition of the DDI or for taking the appropriate action to prevent the risk of an adverse outcome. Computerized drug interaction surveillance systems may be helpful in detecting and preventing DDI with clinical significance. However, many pharmacists and doctors experience these systems to yield a large number of alerts with questionable or unclear clinical significance (suboptimal specificity), fail to provide identifiable patient and medication risk factors, fail to detect all relevant DDI (suboptimal sensitivity) and to include a variable set of DDI [22-25]. These problems stress the importance of transparency and selectivity in choosing the DDI to be included in computerized drug interaction surveillance systems on the basis of a structured assessment procedure.

Chapter 5 concerns the DDI aspect of drug safety. **Chapter 5.1** describes the procedures for structured assessment of DDI and the translation of this assessment to the computerized drug interaction surveillance system by the Working Group on Pharmacotherapy and Drug Information in the Netherlands. Further, this chapter presents results of the revision of the complete computerized drug interaction surveillance system of the Royal Dutch Association for the Advancement of Pharmacy on the basis of these assessments. In **chapter 5.2** an overview is given of potential DDI with disease-modifying antirheumatic drugs (DMARD), to assess the clinical relevance of potential DDI with DMARDs and to study the uniformity in assessment of clinical relevance between rheumatologists and hospital pharmacists.

Objectives of the thesis

The objective of this thesis is to study aspects of safety and effectiveness of pharmacotherapy in the treatment of rheumatoid arthritis, with focus on leflunomide and parenteral gold. Furthermore, in this thesis the assessment of the clinical relevance of drug-drug interactions with DMARDs is studied.

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Chapter 2

Practice research with leflunomide

Chapter 2.1

Leflunomide in active rheumatoid arthritis. A prospective study in daily practice.

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Abstract

Objectives

We prospectively studied the effectiveness, incidence of adverse drug reactions and withdrawal from leflunomide in an outpatient population with rheumatoid arthritis in a setting of care-as-usual.

Methods

In this prospective case series study, from outpatient medical records a standard dataset was collected including patient and disease characteristics, data on leflunomide use and adverse drug reactions.

Results

During the study period 136 rheumatoid arthritis patients started leflunomide. Median (range) follow-up duration was 317 (11-911) days. Sixty-five percent of patients experienced at least one adverse drug reaction related to leflunomide. During follow-up 76 patients (56%) withdrew from leflunomide treatment, mainly because of adverse drug reactions (29%) or lack of effectiveness (13%). The overall incidence density for withdrawal from leflunomide was 56.2 per 100 patient years. Complete data for calculating effectiveness using a validated disease activity score on 28 joints (DAS_{28}) was available for 48, 36, and 35% of patients at 2, 6, and 12 months follow-up, respectively. Within a 12-month period after start of leflunomide treatment 76% of the evaluable patients were classified as moderate or good responder according to the DAS_{28} response criteria.

Conclusions

In the setting of care-as-usual rheumatoid arthritis patients starting leflunomide frequently experienced adverse drug reactions. More than half of the patients withdrew from leflunomide treatment within a year after start of leflunomide treatment, mainly because of adverse drug reactions.

Introduction

In January 2000 leflunomide was registered in The Netherlands for treating active rheumatoid arthritis (RA). Leflunomide represents a novel class of disease-modifying antirheumatic drugs (DMARDs), the isoxazole derivatives. The active metabolite, A77 1726, reversibly inhibits the enzyme dihydroorotate dehydrogenase, the rate limiting step in the *de novo* synthesis of pyrimidines [1]. Hypotheses on the pathogenesis of RA suggest an important role of activated T lymphocytes [2]. Since lymphocytes are dependent on *de novo* synthesis of pyrimidines for their cell division, proliferation of lymphocytes is inhibited by A77 1726.

Efficacy and safety of leflunomide has been demonstrated in randomized controlled trials that included over 1000 RA patients treated with leflunomide [3-10]. These trials demonstrate similar efficacy of leflunomide in suppressing RA as compared with sulfasalazine and methotrexate (MTX) after 6 months to two years of follow-up [3-7]. By inclusion of patients based on selection criteria and strict follow-up, the trial setting is different from daily clinical practice in rheumatology. This difference between research trial and day-to-day practice, may limit the validity of extrapolation of data from these trials to RA patients in daily practice [11]. Therefore, studies on clinical experience in daily practice with newly approved therapies are important to inform about potential discrepancies with the results from randomized controlled trials.

In this study we evaluated the effectiveness, safety and withdrawal rates for leflunomide in an outpatient RA population treated with usual care.

Methods

Patients and inclusion criteria

All consecutive RA patients to whom leflunomide was prescribed *de novo* by their rheumatologist in the outpatient departments of rheumatology in Friesland (in the Northern part of the Netherlands) from January 2000 to June 2002 were included. The study was approved by the institutional review board of the Medical Centre Leeuwarden. Patients signed informed consent for collecting a standard dataset using outpatient medical records and were followed from the start of leflunomide until the end of the study, withdrawal from leflunomide or death.

Patients were recorded as ‘lost-to-follow-up’ where the last visit to the outpatient rheumatology department was more than one year ago.

Data collection

The standard dataset, using outpatient medical records, consisted of patient characteristics, disease characteristics, adverse drug reactions (ADRs) and leflunomide use data. During the study period information on leflunomide treatment in combination with other DMARDs was scarce. However, to gain insight in combination of leflunomide with other DMARDs or systemic corticosteroids, data on co-medication were recorded in the study database.

Intensity of follow-up of the patients during this study was similar to non-study patients, reflecting care-as-usual. Patients visited the rheumatologist on a routine basis at least every month up to 6 months after start of leflunomide treatment and every 2 months thereafter. During these visits a routine physical examination was conducted, parameters for calculation of the disease activity score on 28 joints (DAS28) were scored, and ADRs were collected. In case of intercurrent problems, patients contacted the outpatient department by telephone. In the outpatient medical records all telephone contacts were registered.

An exception to the rule of care-as-usual was made for registration of parameters necessary for calculation of the Disease Activity Score using 28 joints (DAS_{28}), a validated score for establishing disease activity and response to therapy in RA [12,13]. The DAS_{28} is calculated from four parameters: the number of swollen and tender joints from a total of 28 joints, the erythrocyte sedimentation rate and the visual analogue score for general health as subjectively estimated by the patient. High, moderate or low disease activity is categorized as DAS_{28}-scores >5.1, >3.2 but ≤5.1 and >2.6 but ≤3.2, respectively. Remission is categorized as DAS_{28}-scores ≤ 2.6 [12]. Response to treatment according to DAS_{28} is defined by both the difference in DAS_{28} and the DAS_{28} achieved (Table 1).

To avoid bias of DAS_{28} on treatment decisions during the study period, DAS_{28} was calculated from the individual parameters only at the end of the follow-up. Due to possible incompleteness of DAS_{28} data we predefined the category of evaluable patients for response on leflunomide treatment as patients for whom a DAS_{28} at start of leflunomide, and at least 1 follow-up DAS_{28} in the first 12 months of leflunomide treatment was available. DAS_{28}-response was categorized comparing the DAS_{28} at start of leflunomide treatment with the lowest DAS_{28} achieved during the first 12 months.

During each follow-up visit patients were asked about ADRs. When an ADR or abnormal biochemical parameter was encountered and judged by the rheumatologist or patient as possibly related to leflunomide, then the ADR was recorded. Different ADRs reported by one patient although possibly related to each other, were recorded as separate ADRs (for example weight loss in combination with loss of appetite, nausea or vomiting). Serious ADR

Table 1. Definition of DAS_{28} responder categories.

DAS_{28}-calculation: $DAS_{28} = 0.56* \sqrt{TJS_{28}} + 0.28*\sqrt{SJS_{28}} + 0.70*\ln ESR + 0.014\ VAS_{general\ health}$

		Change in DAS_{28}	
DAS_{28} achieved	>1.2	>0.6 -≤1.2	≤0.6
≤3.2	good	moderate	non
>3.2- ≤5.1	moderate	moderate	non
>5.1	moderate	non	non

Legend: DAS_{28} = Disease Activity Score on 28 joints; ESR = Erythrocyte Sedimentation Rate (mm/hr); SJS_{28} = Swollen Joint Score for 28 joints; TJS_{28} = Tender Joint Score for 28 joints; VAS = Visual Analogue Scale (mm).

were predefined as fatal, life-threatening, permanently disabling or necessitating hospital admission.

Withdrawal from leflunomide was defined as any reported discontinuation of leflunomide use. In the study database the reasons for withdrawal from leflunomide treatment were recorded using the information in the medical record. If no specific reason for withdrawal was mentioned, this was recorded in the study database as such.

In case of restarting leflunomide, patients were not eligible for re-entry into this study. To detect restart of leflunomide, patients were followed for another 12 weeks after withdrawal from leflunomide.

Leflunomide treatment

The place of leflunomide in the sequence of DMARD therapy in RA is not standardised, and was left to the judgement of the individual rheumatologist. Leflunomide was prescribed in a dose as recommended by the manufacturer, i.e. loading dose of 100 mg daily for 3 days, followed by 20 mg daily.

Statistical analyses

Access database software (Microsoft Corp.) was used for data collection, data validation and data selection. SPSS 10.0 for Windows (SPSS Inc, Chicago, Ill, USA) was used for statistical analysis. For survival analysis the Kaplan-Meier estimator was used to calculate the cumulative probability of withdrawal from leflunomide.

Results

Population

All consecutive RA patients to whom leflunomide was prescribed during the study period were included, leading to a study population of 136 patients. Reasons for starting leflunomide were: ADRs on previous DMARD-therapy (n=26; 19%), ineffectiveness of previous DMARD (n=63; 46%) or a combination of these reasons (n=17; 13%). For 3 (2%) patients the specific reason for starting leflunomide was not registered in the files and 27 patients (20%) started leflunomide as the first DMARD.

Table 2 shows baseline demographic and clinical characteristics of our study population and characteristics from the populations from the major randomized controlled trials [3-5]. Median (range) follow-up duration was 317 (11-911) days. Three patients died during follow-up from a natural cause, i.e. not related to leflunomide use and 8 patients were lost to follow-up.

Four patients (3%) started leflunomide in combination with MTX in order to bridge the first months, in which leflunomide was not expected to show optimal effectiveness. Three of these patients were withdrawn from MTX within 6 months after start of leflunomide as planned and 1 patient continued using the combination. For 15 patients (11%) another DMARD was added to leflunomide treatment (8x MTX, 5x hydroxychloroquine, 1x sulfasalazine, 1x infliximab) during follow-up. From these patients 7 withdrew from leflunomide (3x for reason of ADR (all MTX-combinations), 2x ineffectiveness (1 MTX and 1 sulfasalazine combination) and 2x combination of ADR and ineffectiveness (both MTX-combination)), 2 were lost to follow-up, 1 patient died.

Effectiveness and adverse drug reactions

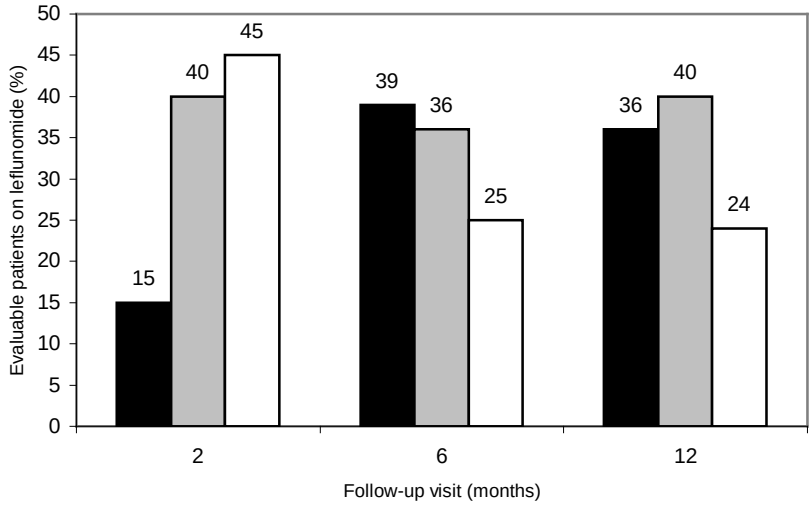
Due to incomplete data for calculating DAS_{28}, disease activity and response category data were not available for every patient at every visit. At baseline for 79 of 136 patients (58%) a DAS_{28} could be calculated. Complete DAS_{28}-data were available for 48, 36, and 35% of patients at 2, 6, and 12 months follow-up, respectively.

Table 2. Baseline demographic and clinical characteristics of the present study population on leflunomide compared with [3-5].

Demographic characteristics	*Present study*	*[3][1]*	*[4]*	*[5]*
Number of patients	136	133	182	501
Age (yrs)				
Mean [SD]	65 [13]	58 [11]	54 [12]	58 [10]
Range	27-89			
> 65 years (%)	47			31
Female (%)	66	76	73	71
Rheumatoid factor positive (%)	80	79	65	
Duration of RA (yrs)				
Mean [SD]	9.7 [11.2]	7.6 [8.6]	7.0 [8.6]	3.7 [3.2]
Range	0.1-60			
≤ 2 years (%)	33	38	39	44
Previous DMARD treatment (%)	76	60	56	66
DMARDs failed (n)				
Mean [SD]	1.7 [1.5]	1.2	0.8 [1.0]	1.1 [1.1]
Range	0-6			
DAS_{28}				
Mean [SD]	5.25 [1.01]			
Median [Range]	5.32 [2.4-8.4]			
Last DMARD prior to leflunomide (n(%))				
Methotrexate	40 (30)			
Sulfasalazine	28 (22)			
Hydroxychloroquine	22 (17)			
Other	14 (10)			
Concomitant systemic corticosteroids (n(%))	59 (43)	29	54	36
< 7.5 mg prednisone equivalents daily	46 (33)			
≥ 7.5 mg prednisone equivalents daily	13 (10)			

Legend: DMARD= disease-modifying antirheumatic drug; SD = standard deviation. [1] Data after 12 month follow-up.

Figure 1. DAS_{28} responders at 2-, 6- and 12-month follow-up visit (% of patients).



Patients at risk	124	99	72
Evaluable patients			
n	60	36	25
%	48	36	35

Legend: Good responders; Moderate responders; Non-responders

Ninety-eight percent of the evaluable patients had high or moderate disease activity according to DAS_{28} criteria at baseline. Two percent of the patients started leflunomide treatment with a baseline $DAS_{28} \leq 2.6$. Responder categories according to DAS_{28}-criteria at the 2, 6 and 12 month follow-up visits are shown in Figure 1.

During follow-up in 89 patients (65%) at least one ADR was registered. Table 3 lists the ADRs reported by 3 or more patients (>2%) during follow-up. All patients reporting weight loss also report loss of appetite or diarrhea. Loss of appetite does not seem to be directly correlated to other gastrointestinal complaints, since only 3 of 6 patients who report loss of appetite also report diarrhea (3x) and/or nausea (1x).

For one patient a serious adverse event was recorded leading to hospitalization. This patient, who was one of the 9 patients developing hypertension, suffered an ischemic cerebrovascular accident during leflunomide treatment.

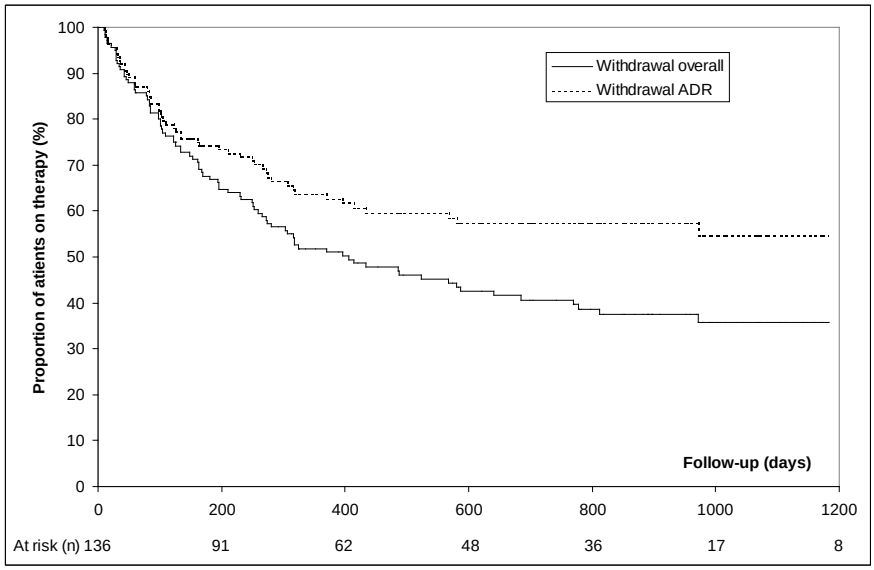
Table 3. Percentage of patients reporting adverse drug reactions (>2% of patients in present study) and associated withdrawal rates, in comparison with [4,5].

	Present study			*[4]*		*[5]*	
	ADR		*Withdrawal*	*ADR*	*Withdrawal*	*ADR*	*Withdrawal*
	n	*%*	*%*	*%*		*%*	
Withdrawal (per patient year follow-up)							
Overall			56.2		30		47
ADR			29.6		19		22
Ineffectiveness			12.6		7		4
Combination of ADR and ineffectiveness			7.4				
Other			6.7		4		8
ADR							
diarrhea	40	29.4	18.4	33.5	5.5[1]	18	2
nausea	15	11.0	5.9	20.9[2]		11.2	1.2
pruritus	10	7.4	4.4				
hypertension	9	6.6	4.4	11	1.1		
skin problems[3]	8	5.9	3.7		2.2	7.4	1.2
alopecia	7	5.1	2.9	9.9	0.5	16.6	1.4
gastrointestinal pain	7	5.1	2.2	13.7		5.6	0.8
abnormal enzyme elevations[4]	6	4.4	3.7	11	7.1	5.4	1.6
loss of appetite	6	4.4	2.2				
headache	4	2.9	1.5			6.2	0.6
vomiting	3	2.2	2.2				
hoarseness	3	2.2	2.2				
weight loss	3	2.2	1.5				
mouth ulceration	3	2.2	0.7	6.0		3.0	0.2

Legend: ADR = adverse drug reaction, ALT = Alanine AminoTransferase, AST = Aspartate AminoTransferase.

[1] Withdrawal for all gastrointestinal ADR; [2] Nausea and vomiting; [3] ADR skin events reported (n): eczema (2), rash (2), psoriasis (1), urticaria (1), dry skin (1), not specified (1); [4] Abnormal plasma liver enzyme levels are defined as ALT or AST values > 2x upper limit of normal values, reference [5] > 3x upper limit of normal values.

Figure 2. Kaplan-Meier for withdrawal from leflunomide-use.



Additionally, the following ADRs were reported with a frequency of <2% of the patient population: fatigue (n=2), polyuria, nocturnal enuresis, tinnitus, dry mouth, constipation, palpitations, dry eyes, lightheadedness, tremor, excessive perspiration, anxiety, swollen lips, muscle cramps in lower legs, coughing, nailfold laesions, thrombocytopaenia (nadir 75 x 10^9/L), and dizziness (all n=1).

Withdrawal from leflunomide

During follow-up 76 patients (56%) withdrew from leflunomide treatment. Fifty percent of study patients withdrew from leflunomide within 405 days. The incidence density for withdrawal from leflunomide was 56.2 per 100 patient years. Figure 2 shows Kaplan-Meier estimates of the proportion of patients withdrawing from leflunomide during follow-up. Reasons for withdrawal from leflunomide were ADRs (n=40; 29%), ineffectiveness or loss of effectiveness (n=17; 13%) or a combination of ADR and insufficient effectiveness (n=10; 7%). Two patients (1.5%) stopped leflunomide for comorbidity not related to leflunomide treatment (sepsis, toxic megacolon). For 7 patients (5%) no specific reason for stopping leflunomide was recorded. Table 3 shows the frequencies of withdrawal from leflunomide for

ADRs recorded for 3 or more (>2%) patients during follow-up in our study and two randomized controlled trials with 12 month follow-up data [4,5].

Within 12 weeks after withdrawal from leflunomide 7 patients out of 76 (9%) restarted leflunomide and 6 of these patients were still on leflunomide treatment at the moment of closing the study database (January 2003). Reasons for stopping leflunomide before restarting at a later date were ADR for 4 patients, ineffectiveness for 1 patient, and a combination of ADRs and ineffectiveness for 2 patients.

Discussion

Data from randomized controlled trials are obtained from selected populations in the setting of a strict follow-up. A follow-up study of patient populations outside the setting of a randomized controlled trial is an important tool to learn about drug effectiveness and safety in daily clinical practice. Leflunomide has become available for the treatment of RA in a period of new treatment possibilities for RA and a changing treatment algorithm. Early treatment of RA with DMARDs [14], the availability of tumor necrosis factor-alpha antagonists [15,16] and the use of DMARDs in combination therapy [17] highlight the need for careful evaluation of new treatment options. In this study we followed an outpatient population that started leflunomide for the treatment of RA in the setting of care-as-usual.

Some remarks should be made on the limitations of the present study. Firstly, for only 35-58% of the patients on leflunomide therapy at every visit a DAS_{28}-score could be calculated due to missing data. Although we expected some incompleteness of DAS_{28}-data before start of the study and we prospectively defined patients that could be evaluated, the influence of missing data on overall response rates is not clear. The percentage of DAS_{28}-non-evaluable patients reflects one of the basic concepts of the study. In our study we follow an outpatient population of patients, consecutively starting leflunomide treatment for their RA in a setting of care-as-usual. Since optimization of completeness of DAS_{28} data would require serious interference with the concept of care-as-usual, and therefore with clinical decision making, it was explicitly decided at the start of the study not to interfere during follow-up.

Secondly, this study was conducted in the period immediately following leflunomide licensing for the treatment of RA. The role of leflunomide in the treatment algorithm of RA is not yet defined and may well change in time. This is illustrated by the results of studies combining leflunomide with MTX [8,18]. This changing place of leflunomide in the treatment

of RA may have consequences for patient outcomes in terms of treatment effectiveness or safety and the applicability of our study results in the future.

At baseline 98% of our evaluable study population had high or moderate RA disease activity according to DAS_{28}-criteria [12]. This percentage reflects high adherence of the rheumatologists to the approved indication of leflunomide for adult patients with active RA. During the first 12 months of follow-up the percentage of non-responders per visit varied from 24-45%. Despite this large percentage of non-effective treatment, overall only 13% withdraw from leflunomide treatment because of ineffectiveness. This discrepancy may be explained by the fact that DAS_{28}-scores are not used in routine clinical practice in our centre as key parameter for treatment effectiveness. Another explanation may be the strategy of postponing withdrawal in the expectation of effectiveness later during treatment. This strategy is supported by data from recent studies. Results of randomized controlled trials [3,4] show improvement of disease severity characteristics for an increasing percentage of the study population in the period from 3 to 6 months after start of leflunomide treatment. Dougados et al [19] in their 6 month follow-up data from the RELIEF study, show an increase of 56.0 to 77.1% in patients achieving a 'definitive' responder rate at week 12 and 24 of leflunomide treatment, respectively.

Comparison of our results with randomized controlled trials, Strand et al [4] and Emery et al. [5] in their studies found 52%, respectively 50.5% of patients reaching 20% improvement according to the criteria of the American College of Rheumatology (ACR20) after 12 months. In our study 76% of evaluable patients show moderate or good response at 12 month follow-up according to DAS_{28}-criteria. Although degrees of responder categories according to DAS_{28}- and ACR20-criteria correlate well [20,21], comparison of our results with randomized controlled trials is not possible due to incompleteness of our data on DAS_{28}-scores.

In the past few years, despite the availability of leflunomide and the biologicals, the treatment algorithm for RA did not change significantly. Therefore, the place of leflunomide in the treatment strategy of RA in the past few years was often secondary to other DMARDs. Its place in therapy is reflected by the baseline characteristics of our study population.

Compared with the population included in the randomized controlled trials on leflunomide our population is older, has a longer duration of RA, and is more frequently and more intensively treated with DMARDs before start of leflunomide. Major inclusion criteria from the randomized controlled trials were a duration of RA >4-6 months [4,5], an age over 18 years, active disease, and no concomitant DMARD-therapy [3-5]. Concomitant use of systemic corticosteroids (≤ 10 mg prednisolone daily or equivalent) was allowed if doses were stable

for 4 weeks previous to leflunomide start. In our study at baseline 89% of patients had a disease duration over 4 months, all patients were over 18 years of age (range 27-89), 98% had active disease and 86% used leflunomide as the only DMARD during complete follow-up. In our population 30% of patients switched from MTX to leflunomide, in contrast, in the study by Strand et al [4] patients who were pretreated with MTX were not eligible. This pretreatment with MTX could influence comparability of data with the present study. However, MTX pretreatment as risk factor for early leflunomide withdrawal or reduced effectiveness has not been published to our knowledge. Overall, the in- and exclusion criteria used in the randomized controlled trials [3-5] are not different from the characteristics in the present study population.

The ADR reported in our study are in general comparable with the ADR reported in randomized controlled trials. However, in our study hoarseness and loss of appetite (independent of other gastrointestinal complaints) are reported in >2% of patients. These ADRs are not reported in the randomized controlled trials [3-5].

Compared with randomized controlled trials with approximately the same duration of follow-up as the present study [4,5] the overall withdrawal rate is high in our study, 56.2 per 100 patient years. Withdrawal due to ADRs represent approximately 50% of the overall withdrawal rate both in our study and in the randomized controlled trials.

Results of studies outside the setting of randomized controlled trials show high withdrawal rates for leflunomide treatment. Geborek et al [22] report withdrawal from leflunomide treatment of 78% of patients after 20 months follow-up. Siva et al [23] and Hajidiacos et al [24] report withdrawal rates of 63% and 78%, respectively, after 6 months of follow-up. After 12 months withdrawal rates of 48% [24] and 57% [25] have been reported. Wolfe et al [26] report failure rates of 55.5% per 100 patient years follow-up. The results from these observational studies and the present study suggest that the withdrawal rate from leflunomide treatment is higher in the setting of care-as-usual compared with randomized controlled trials.

The high withdrawal rates demand optimization of the leflunomide treatment schedule and better recognition of patients at risk for treatment failure. Possibilities for improvement of the treatment schedule include omitting the loading dose, weekly dosing and/or titration of the leflunomide dose on the basis of the plasma concentrations of the active metabolite, A77 1726.

Siva et al [23] present evidence for the higher risk (odds ratio 2.0, confidence interval 1.76-2.4) of leflunomide treatment failure after start with the 3x100 mg loading dose

compared with no loading or other loading schemes. Erra et al [27] in their study conclude a potential association between the loading dose and early adverse events. Several studies investigated weekly dosing of leflunomide [28,29]. Although these studies are small and have a short duration of follow-up, the results suggest that weekly dosing of leflunomide is effective and well tolerated.

The relationship between mean steady-state plasma concentrations of A77 1726 and the probability of clinical success [30] suggest options for therapeutic drug monitoring and dose titration. Since leflunomide dosing is limited to 20 mg daily with possible dose reduction to 10 mg [31], at the moment the possibilities for dose adjustment are scarce. On the basis of study results thus far, the abovementioned options for adaptation of the dosing schedule of leflunomide have to be explored in future research in order to optimize leflunomide treatment.

Conclusion

Leflunomide offers an efficacious treatment option although the incidence of withdrawal from leflunomide therapy in the present study was high. ADRs are the most frequently encountered reason for withdrawal. The results of this study stress the importance of critical evaluative studies in the positioning of a novel DMARD in the setting of care-as-usual.

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Chapter 2.2

Leflunomide for rheumatoid arthritis in clinical practice. Incidence and severity of hepatotoxicity.

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Abstract

Objectives

Leflunomide is a novel disease-modifying antirheumatic drug. Because of reports on possible hepatotoxicity and adaptations in the recommendations for monitoring liver function during leflunomide treatment, we conducted a study to evaluate the incidence and severity of hepatotoxicity.

Methods

We included consecutive, rheumatoid arthritis patients starting treatment with leflunomide in the region of Friesland (The Netherlands) between January 2000 and January 2002. During follow-up patient characteristics, disease characteristics, and clinical and laboratory data on liver functions were registered. Severity of hepatotoxicity was categorized using the National Cancer Institute Common Toxicity Criteria, as moderate (grade 2), severe (grade 3) or life threatening (grade 4).

Results

101 patients were followed for a median period of 10 months (range 0.5-12). Grade 2 or 3 elevations in any liver function blood test were recorded for 9 patients (8.9%). No grade 4 elevations were recorded. Four patients (4%) showed grade 2-3 aminotransferase elevations. Due to grade 2 hepatotoxicity one patient (1%) was withdrawn from leflunomide treatment, and one patient continued leflunomide in a reduced dose. In eight of nine patients with grade 2-3 liver function blood tests, these elevated liver function tests occurred within 6 months after starting leflunomide. None of the patients with grade 2 or 3 toxicity had a history of hepatic disease, eight patients concomitantly used potential hepatotoxic co-medication. Eight (8%) patients used leflunomide in combination with methotrexate, one of these patients developed hepatotoxicity. No clinical signs of serious hepatotoxicity were recorded during follow-up.

Discussion

In 8.9% of the patients grade 2 or 3 hepatotoxicity was recorded within the first year after start of leflunomide therapy based on liver enzyme determinations. In the majority of the patients liver enzyme elevations occurred within the first 6 months of therapy and resolved during continued follow-up. None of the patients showed clinical signs of hepatotoxicity.

Conclusion

Under continued monitoring of liver functions hepatotoxicity during leflunomide use does not seem to be a major problem in our population.

Introduction

Leflunomide is an isoxazole-derived disease-modifying antirheumatic drug (DMARD). Leflunomide is a prodrug that is converted in the gastrointestinal tract and plasma to its active metabolite A77 1726. The primary mechanism of action of A77 1726 is inhibition of the enzyme dihydroorotate dehydrogenase, a key enzyme in the *de novo* pyrimidine synthesis. Activated T-lymphocytes, which are believed to play a central role in the pathogenesis of rheumatoid arthritis (RA), depend on *de novo* pyrimidine synthesis for proliferation. Efficacy and safety of leflunomide has been demonstrated in several randomized controlled trials [1-3].

Elevated liver function tests during treatment with leflunomide in patients with RA have been reported in randomized controlled trials studying leflunomide monotherapy in comparison with methotrexate or sulfasalazine [1-3]. After registration of leflunomide, the European Agency for the Evaluation of Medicinal Products (EMEA) in 2001 published a Public Assessment on rare, serious cases of hepatotoxicity during use of leflunomide. Reasons for the publication of this Public Assessment were 15 cases with fatal outcome and reported liver failure, liver toxicity, hepatitis, cholestatic jaundice or increased liver function tests over more than 100,000 patient years of leflunomide exposure. In 10 of the 15 cases an hepatic event was not the immediate cause of death. The reported cases were complicated by associated factors possibly leading to poor outcome, such as pre-existing liver disease, pre-existing/concurrent illness or comorbidity (heart failure, infection/sepsis, pulmonary failure, pancreatitis) and other possibly hepatotoxic co-medication.

The discussion on potential hepatotoxicity of leflunomide led to adaptations in the Summary of Product Characteristics and the package leaflet stressing the importance of monitoring of liver functions. The current recommendations are Alanine AminoTransferase (ALT) must be checked before initiation and at least at monthly intervals during the first 6 months of treatment and every 8 weeks thereafter. For ALT elevations between 2- and 3-fold the upper limit of normal (ULN) values (as defined by the local laboratory), dose reductions from 20 mg to 10 mg may be considered and monitoring must be performed weekly. If ALT elevations >2 x ULN persist or if ALT of >3 x ULN are present, leflunomide must be discontinued and washout initiated.

Observational cohort studies performed after registration of a novel medication regimen can help to establish the effectiveness and safety of leflunomide in a setting similar to daily clinical practice. Therefore, to gain insight in the timing, frequency and severity of elevated

liver enzymes or clinical hepatotoxicity and to aid in clinical decision-making, we conducted a study on the incidence and severity of hepatotoxicity during leflunomide treatment in a cohort of RA patients in a setting of 'care-as-usual'.

Methods

Patients and inclusion criteria

All consecutive RA patients who were prescribed leflunomide *de novo* by their rheumatologist in the outpatient departments of rheumatology in Friesland (in the Northern part of the Netherlands) from January 2000 to January 2002 were included. The human research committee approved the study, and written informed consent was received from all subjects in the study. Patients were followed from the moment they started leflunomide therapy for a period of 12 months, unless they withdrew from leflunomide therapy or died. The standard dataset consisted of patient characteristics, disease characteristics, parameters of disease activity (disease activity on 28 joints; DAS_{28}) [4], and laboratory data on liver function.

Intensity of follow-up of the patients during this study was not different from non-study patients in our outpatient departments of rheumatology, reflecting care-as-usual. Patients visited the rheumatologist every 4-8 weeks for the first 6 months after initiation of leflunomide therapy. Depending on the judgement of the rheumatologist the frequency of visits after 6 months was reduced to at least every 6 months. With laboratory controls, including hepatic enzyme determination, every 8 weeks.

During visits a routine interview and physical examination, including collection of DAS_{28}-parameters, took place. In the case of problems the outpatient department of rheumatology could be reached by telephone. Every telephone contact was registered in the outpatient medical records.

During follow-up visits patients were asked about adverse events. When an adverse event or an abnormal biochemical parameter was encountered and judged by the rheumatologist or patient as possibly related to leflunomide use, then the adverse event was recorded in the study database. All liver enzyme determinations during the 2-year study period were recorded and used for analysis.

Medication

Leflunomide was prescribed by the participating rheumatologists on the basis of good clinical practice for their individual patients in a dose as recommended by the manufacturer: starting with a loading dose of 100 mg daily for 3 days, followed by 20 mg daily.

Clinical and outcome measures

Clinical data on hepatotoxicity (hepatitis, jaundice, (pre)coma hepaticum) were collected from outpatient and hospital medical records. Since the reports on hepatotoxicity of leflunomide involved both hepatocellular injury and cholestatic adverse events, laboratory data on the enzyme activities of Alanine AminoTransferase (ALT), Aspartate AminoTransferase (AST) as well as Alkaline Phosphatase (AP), Gamma GlutamylTranspeptidase (GT) and Total Bilirubin (TB) were collected. With respect to the moment of occurrence of the hepatotoxicity event, four time frames were defined, based on the start of leflunomide treatment.

- Period I consisted of the time from 6 months prior to the start of leflunomide until the start of leflunomide.
- Periods II consisted of the time period during leflunomide treatment from 1 week to 1 month
- Period III consisted of the time period during leflunomide treatment from 1-6 months
- Period IV consisted of the time period during leflunomide treatment from 6-12 months after start of leflunomide.

In the case of more than one known laboratory value for one parameter in a specific period the value most deviating from the ULN was recorded in the database. Laboratory values on liver enzyme activities were categorised according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, see Table 1). Primary outcome measures, with general NCI-CTC definitions, were grade 2 (moderate adverse event), grade 3 (severe and undesirable adverse event) or grade 4 (life-threatening or disabling adverse event) toxicity according to NCI-CTC.

The ULN of a given liver enzyme activity is defined as the mean of the distribution + 2 standard deviations of a presumably representative healthy population. It has to be taken into account that, by definition, 2.5% of healthy individuals will have an abnormal elevation of a given liver chemistry test [5]. For this reason, and the minor clinical relevance of grade 1 enzyme activity elevations (NCI-CTC description: mild adverse event), we scored only grade 2, 3 or 4 liver enzyme elevations.

Table 1. NCI-CTC categories for liver enzyme elevations.

	Toxicity grade (NCI-CTC)				
	0	*1*	*2*	*3*	*4*
Description[1]	WNL	≤ 2.5 x ULN	>2.5-≤ 5 x ULN	>5-≤ 20 x ULN	> 20 x ULN
Description for TB	WNL	-	<1.5 x ULN	≥1.5-< 3 x ULN	≥ 3 x ULN
Clinical relevance of hepatotoxicity	None	Mild	Moderate	Severe	Life-threatening/ disabling

Legend: TB = total bilirubin, NCI-CTC = National Cancer Institute - Common Toxicity Criteria, ULN = upper limit of normal value, WNL=within normal limit. [1]Description of NCI-CTC categories for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and gamma glutamyltranspeptidase (GT).

For patients with grade 2-4 elevations of liver enzyme activities in any time period during leflunomide treatment (II-IV) the medical records were screened for pre-existent hepatic disease, or potential hepatotoxic co-medication. Co-medication was regarded as potentially hepatotoxic when liver toxicity was mentioned in Meyler's Side Effects of Drugs [6]. Alcohol intake was not scored during the study.

As AP and GT may behave as acute phase proteins and, therefore, may result from an active inflammatory process, the correlation between DAS_{28} and AP or GT activities is calculated.

Statistical analyses

Access database software (Microsoft Corp.) is used for data collection and selection. SPSS 10.0 for Windows is used for descriptive statistics.

Results

During the study period, clinical and laboratory data on hepatotoxicity are recorded for 101 patients who began leflunomide therapy with a median follow-up of 10 (range 0.5-12) months (see Table 2). Due to variable follow-up (i.e. not all patients had liver enzyme levels determined in all periods) and withdrawal of leflunomide, the number of patients for whom

Table 2. Patient characteristics.

Demographic characteristics		
Number of patients		101
Age (yrs)		
	Mean (SD)	65.1 (12.9)
	Range	27-89
Female (%)		65
Rheumatoid factor positive (%)		77
Duration of RA (yrs)		
	Mean (SD)	10.3 (11.9)
	Range	0.1-60
Clinical characteristics		
Previous DMARD treatment (%)		82
Number of previous DMARDs		
	Mean ± SD	1.7 (1.4)
	Range	0-6
Concomitant systemic corticosteroids (n(%))		
	None	55 (54)
	< 7.5 mg prednisone equivalents daily	29 (29)
	≥ 7.5 mg prednisone equivalents daily	17 (17)

Legend: DMARD = disease-modifying antirheumatic drug, LEF = leflunomide; SD = standard deviation, yrs = years.

liver function blood tests could be evaluated for periods I, II, III or IV vary from 101, 68, 81 and 55, respectively.

Of the 101 patients enrolled over the 2 years of the study, a total of 38 patients (38%) withdrew from leflunomide treatment. Reasons for withdrawal were given as: adverse drug reactions (n=23;23%; 22 of these withdrawals were due to non-hepatic events and one due to grade 2 elevations of liver enzymes), ineffectiveness (n=5;5%), combination of inadequate effectiveness and adverse drug reactions (n=7;7%) or other reasons (3;3%).

In total 997 liver function blood tests were recorded during the 2-year study period, with 316, 190, 290 and 201 test results in periods I to IV, respectively. Throughout the 2-year study period no clinical signs of severe hepatotoxicity have been registered.

During period I, before start of leflunomide treatment, no patients had grade 2 or 3 ALT or AST elevations and three patients had grade 2 or 3 AP and/or GT elevations. None of these latter patients show further elevation of AP/GT-activities during follow-up.

In total, during follow-up 9 patients (8.9%; CI95 3.2-14.6%) show grade 2-3 elevations in liver enzyme activities (see Table 3). Of these, maximal deviations from ULN were grade 3 elevations for 3 patients and grade 2 elevations for 6 patients. None of the patients with grade 3 elevations withdrew leflunomide therapy for the reason of hepatotoxicity. One of these patients showed spontaneous regression of ALT elevations in period III (grade 2) and period IV (grade 1); for two patients with grade 3 GT elevations, these elevations were present throughout complete follow-up. Abdominal ultrasound scans were performed for 2 of the 3 patients with grade 3 elevations, showing no evidence for pathology. No liver biopsies were performed for any of the patients with grade 3 elevations. No grade 4 toxicity was recorded.

Concerning the potential risk factors accounted for, none of these patients with grade 2 or 3 elevations have a history of hepatic disease or excessive alcohol consumption. Eight of the 9 patients with grade 2-3 elevations of liver enzyme activities have been treated with other potentially hepatotoxic co-medication concomitantly (6x diclofenac, 1x MTX and 1x flucloxacilline).

During the 2-year study period 8 (8%) patients used leflunomide in combination with MTX. One of these patients developed grade 2 liver enzyme elevations (AP and GT) during combination therapy, which reverted to normal values under continued combination treatment without dose reduction of leflunomide or MTX.

For two patients (2%) the prescription of leflunomide was altered. For one patient the daily leflunomide dose was reduced from 20 mg to 10 mg in period III, due to grade 1 activity elevations of ALT and AST. Transferase activities normalized after dose reduction, but leflunomide was withdrawn due to insufficient effectiveness after 8 months on therapy. For one patient leflunomide was withdrawn on the basis of grade 2 ALT-elevations in period III.

Neither AP nor GT values correlate with DAS_{28}-scores, showing correlation coefficients of 0.002 and 0.06, respectively.

Table 3. Characteristics of patients with grade 2 or 3 liver enzyme elevations.

Patient	*Follow-up duration (months)*	*Liver enzyme determinations*					*Remarks*
		Total[1]	*Abnormal* [2]	*Enzyme*	*NCI*[3]	*Period*	
1	12	7	1	GT	3	4	
2	12	12	6	AP (3x), GT (3x)	3	2	
3	12	16	2	ALT	3	3	
4	3	6	1	GT	2	2	Death, unrelated to treatment
5	12	10	2	ALT/AST	2	3	
6	12	6	1	GT	2	3	
7	12	10	2	ALT/AP	2	3	
8	3	9	1	ALT	2	3	Withdrawn; hepatotoxicity
9	2	7	1	AP	2	2	Withdrawn; mouth ulcerations

Legend: ALT = alanine aminotransferase, AST = aspartate aminotransferase, AP = alkaline phosphatase and GT = gamma glutamyltranspeptidase. [1] Total number of liver enzyme determinations; [2] Total number of grade 2 or 3 elevations for this patient; [3] Highest NCI-CTC category reached.

Discussion

In previous, large, randomized, controlled trials abnormal plasma liver enzyme levels are recorded for patients treated with leflunomide. Emery et al report abnormal plasma liver enzyme levels in 5.4% of patients in their study during the first year of treatment [1]. Strand et al report aminotransferase elevations for 14.8% of patients on leflunomide, all of which are reversible under continued treatment or after treatment withdrawal [2]. The current surveillance of RA patients on leflunomide in the Netherlands gives a valuable estimate of the incidence of hepatotoxicity under conditions of care-as-usual and strict monitoring of liver function tests. In our population the occurrence of grade 2-3 liver enzyme elevations is 8.9%. The incidence of grade 2-3 aminotransferase elevations during leflunomide treatment is 4%. The grade 2-3 elevations of liver enzyme function activities that are recorded in our study, regress to normal under ongoing leflunomide treatment for all except one patient.

Some remarks on the present study have to be made. First, the absence of clinical signs of severe hepatotoxicity and/or grade 4 liver enzyme elevations in our study does not mean that these events cannot occur. Based on our population size the upper limit of the 95% confidence interval of the probability of these events is 2,95%.

Second, the present data do not allow comparison with hepatotoxicity during treatment with DMARDs other than leflunomide. In the setting of 'care-as-usual' this comparison cannot be made since the place of leflunomide in the treatment strategy of RA is different from the place of MTX or sulfasalazine. This may result in treatment of populations with different characteristics and potential confounding of treatment safety results. Despite this consideration the results of the surveillance of Cannon et al. do not show evidence of an increased risk of hepatotoxicity for patients receiving leflunomide compared with other DMARDs [7]. The surveillance of Wolfe et al., however, although not statistically significant, suggest that the rates of hepatic adverse events attributed to leflunomide and MTX were higher than those attributed to other DMARDs [8].

Randomized, controlled trials offer direct comparison of hepatic safety of leflunomide versus other DMARDs in populations with comparable characteristics. Abnormal plasma liver enzyme levels during 12 months follow-up are reported for 5.4% and 16.3% of patients on leflunomide and MTX, respectively, in a randomized controlled trial of these two agents in patients with RA [1]. Aminotransferase elevations are reported in 14.8% and 11.5% of patients treated with leflunomide and MTX, respectively, during 12 months of follow-up [2]. In their recently published systematic review of controlled clinical trials Osiri et al. concluded that elevated liver function tests were not significantly different for the leflunomide-treated patients than for those treated with methotrexate (MTX) or sulfasalazine (SSZ) [9].

Third, the duration of follow-up in our study, similar to the randomized controlled trials, is restricted to a maximum of 12 months [1-3]. A part of the population could not be followed up to this point. Thirty-eight percent of the patients withdrew from leflunomide therapy before 12 months for reasons other than hepatotoxicity, and liver function tests were not available for the complete 12 month period for all patients. Early withdrawal and incompleteness of follow-up leads to 55 of 101 patients for which data on liver enzymes were available after 6 months of follow-up. Furthermore, hepatotoxicity occurring after a period of 12 months is therefore not recorded in our study. Eight of the nine patients (89%) with grade 2-3 liver enzyme elevations in the present study show these elevations within 6 months after start of leflunomide treatment. In three randomized, controlled trials, ALT elevations >3x ULN occurred within 9 months after start of leflunomide treatment in 18 of 23 patients (78%) [1-3].

Two-year follow-up data from these trial populations show no late toxicity or unexpected adverse events after longer duration of leflunomide treatment [10,11]. This suggests that the potential underestimation of liver enzyme activity elevations due to too short follow-up will be minimal.

Fourth, in 8 of 9 patients with liver enzyme elevations potentially hepatotoxic co-medication is used. Hepatotoxicity due to these co-medications or due to a combination of these co-medications with leflunomide cannot be excluded.

Lastly, only 8% of the study patients use leflunomide in combination with MTX. Therefore, results of this study are not applicable for extrapolation to populations using leflunomide in combination therapy. Several studies report on the incidence of elevated liver enzyme activities in patients treated with leflunomide alone or in combination with MTX [12-14]. Kremer et al. conclude that combination treatment of leflunomide and MTX can be used safely with appropriate monitoring of liver enzyme activity [13]. The combination of DMARDs in the treatment of RA may become more important, but information on the place of combination therapy in the treatment paradigm and the preferred combinations still is scarce [15]. Leflunomide monotherapy in RA will therefore remain an important treatment option, leaving the need for extensive data on safety and effectiveness from studies in settings of care-as-usual.

Conclusion

This study presents a critical evaluation and risk assessment on the incidence of hepatotoxicity during leflunomide use in an outpatient setting of care-as-usual. Hepatotoxicity during leflunomide treatment does not seem to present a major problem, under conditions of strict monitoring of liver function.

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Chapter 2.3

Leflunomide in the treatment of rheumatoid arthritis. An analysis of predictors for treatment continuation.

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Submitted

Abstract

Objectives

To determine factors predictive for leflunomide drug survival in an outpatient population with rheumatoid arthritis in a setting of care-as-usual.

Methods

A standard dataset was collected from medical records of consecutive outpatients on leflunomide treatment for rheumatoid arthritis between January 2000 and June 2003. The dataset consisted of patient-, disease- and treatment-characteristics at the start of leflunomide treatment, and data on leflunomide use.

Results

Leflunomide was started in 279 patients and 173 patients (62,0%) withdrew from treatment during follow-up. From univariate analysis, concomitant systemic corticosteroid use and an erythrocyte sedimentation rate < 35 mm/hr at start of leflunomide were found to be predictive for better leflunomide survival. Furthermore, the attending rheumatologist was correlated with leflunomide drug survival. Multivariate analysis suggested attending rheumatologist, concomitant systemic corticosteroid use and erythrocyte sedimentation rate < 35 mm/hr at start of leflunomide to be associated with leflunomide survival.

Conclusions

Concomitant systemic corticosteroid use, erythrocyte sedimentation rate at the start of treatment and attending rheumatologist were found to be predictive for leflunomide survival. Information on these predictors at the start of leflunomide therapy may offer opportunities for treatment optimization.

Introduction

Prescription of new drugs and treatment outcomes may be influenced by channelling bias. Channelling bias occurs when a patient is directed away from or toward a specific therapy because of underlying medical conditions or perceptions of the provider. This phenomenon has to be taken into account when extrapolating the results from randomized controlled trials (RCT) to the setting of care-as-usual, for example in the case of leflunomide treatment for rheumatoid arthritis (RA).

In January 2000 leflunomide was registered for the treatment of active RA on the basis of results from RCTs including over 1000 patients [1-3]. Results of an observational study in patients with RA on leflunomide treatment showed that the characteristics of patients treated in a setting of care-as-usual differ from characteristics of the populations in RCTs suggesting channeling of the application of leflunomide [4]. Compared with the population included in the RCTs on leflunomide the population in this study had a higher age, had longer disease duration, and was more intensively treated with disease-modifying antirheumatic drugs (DMARDs) before starting leflunomide.

Compared with RCTs, reporting withdrawal rates that varied from 30 to 47 per 100 patient years [2,3], observational studies consistently showed higher withdrawal rates, suggesting that channeling influences treatment outcomes in clinical practice. Failure rates have been reported between 55.5% and 56.2% per 100 patient years follow-up [4,5]. Furthermore, Geborek et al [6] and Siva et al [7] reported withdrawal from leflunomide treatment of 78% of patients after 20 months and 63% after 6 months follow-up, respectively. The results from these observational studies suggested that the withdrawal rate from leflunomide treatment is higher in the setting of care-as-usual compared with RCT.

Time remaining on therapy is a relevant factor in obtaining treatment effects, particularly in chronic diseases such as RA. To optimize leflunomide therapy, early recognition of factors predictive for longer treatment survival is of clinical importance. For this reason we performed a study to determine predictors for leflunomide withdrawal in an outpatient population with RA.

Methods

Population

In two regions in the Netherlands (Friesland and Twente) with a total of approximately 1,200,000 inhabitants, consecutive patients starting leflunomide for RA were followed. The study period started in January 2000, the moment leflunomide became available for prescription in the Netherlands, and ended in June 2003.

Leflunomide prescription

At the time this study was conducted the place of leflunomide in the sequence of DMARD therapy in RA was not standardised. Generally, methotrexate was regarded as the option of first choice, and anti-TNF-alpha therapy was available in cases with higher disease activity with proven failure of at least 2 DMARDs. Prescription of leflunomide therefore was left to the judgement of the attending rheumatologist. Leflunomide was prescribed in a dose as recommended by the manufacturer, i.e. a loading dose of 100 mg daily for 3 days, followed by 20 mg daily. In case of adverse events dose reduction to 10 mg daily was an option.

Data collection

Data were collected at every routine visit of the patient to the rheumatologist. The standard dataset, using outpatient medical records, consisted of patient characteristics, disease characteristics, laboratory values and data on leflunomide prescription. Intensity of follow-up of the patients during this study was similar to non-study patients, reflecting care-as-usual.

Withdrawal

Some discontinuations of leflunomide use are temporary, for example in case of intercurrent disease or surgery, and are not related to adverse drug reactions or ineffectiveness of therapy. For this reason the withdrawal from leflunomide was defined as a reported discontinuation of leflunomide for a period longer than 12 weeks. Continuation of leflunomide therapy within this time frame was considered to be a continuation of the first treatment episode and patients were not recorded as ‘withdrawn from therapy’. In case of restarting leflunomide after a period over 12 weeks, patients were not eligible for re-entry into this study.

Predictors

Possible predictors for survival of leflunomide treatment that are continuous variables were studied as continuous and as dichotomous variables. Translation to a dichotomous variable was performed by dividing the population in two groups of equal size.

Statistical analysis

SPSS 12.0.1 was used for data collection, data validation, data selection and statistical analysis. Kolmogorov-Smirnov analysis was used to test for normality. T-test and Mann Whitney tests were used where appropriate, to test for differences between group means of continuous variables. For comparison with respect to categorical variables Fisher's exact test was used. Cumulative probability of survival was estimated using Kaplan-Meier curves.

Differences in time-to-withdrawal for certain factors were investigated using log-rank tests or cox-proportional hazard models, for continuous and categorical variables, respectively. Forward stepwise conditional regression analysis was used for studying variable contribution in multivariate analysis. The independent variables in this analysis were selected on the basis of the univariate analysis. Variables with $p < 0.10$ in univariate analysis were selected for the Cox regression. P-values of 0.05 are considered significant.

Results

Inclusion

Twelve rheumatologists included a total of 279 patients, 140 from the Friesland and 139 from the Twente region. With a median of 21 (range 2-49) patients starting leflunomide per rheumatologist. Baseline demographic and clinical characteristics of the population are shown in Table 1. The dataset was complete, except for 16 and 41 patients for whom no erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at start of leflunomide treatment were recorded, respectively.

Patients were followed for a median period of 9.6 months (range 0.1-38.9 months). In only 3 patients the 3-day 100-mg loading dose was omitted, they started with the daily maintenance dose of 20 mg. Ten patients started leflunomide treatment in combination with methotrexate. None of the patients started leflunomide in combination with other DMARDs.

Table 1. Baseline demographic and clinical characteristics[1]

Characteristic	
Age (years)	62.6 [12.6]
Female (%)	66.7
IgM rheumatoid factor positive (%)	81.4
RA disease duration (yrs ; median[range])	10.0[0-60]
Leflunomide as first DMARD (%)	9.7
DMARDs prior to leflunomide (n; median[range])	3.0 [0-11]
Concomitant systemic corticosteroids (%)	43.0
ESR start (mm/hr)	40 [26]
CRP start (mg/L)	38 [33]
Creatinine (micromoles/L)	78[22]
Dose reduction (%)	16.8

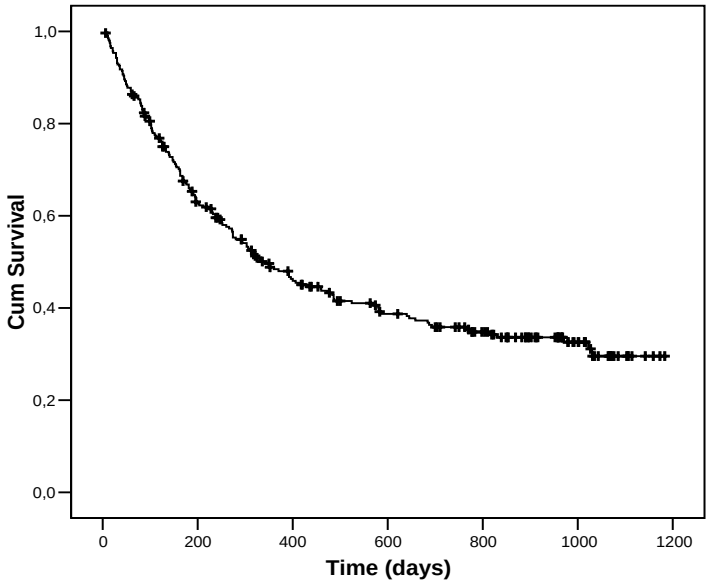
Legend: CRP start = C-reactive protein at the start of leflunomide therapy, DMARD = disease-modifying antirheumatic drug, ESR start = erythrocyte sedimentation rate at the start of leflunomide therapy, RA = rheumatoid arthritis. [1] Values represent mean[SD] unless stated otherwise.

Populations in both centres differed with respect to age, RA disease duration, the number of DMARDs prescribed prior to the start of leflunomide, serum creatinine at start of leflunomide and the fraction of patients for which the leflunomide dose was reduced to 10 mg during follow-up. Other variables did not show significant differences between the two centres. Centre is therefore taken into account as a covariate or stratifier for further analyses. Since attending rheumatologists work exclusively in one of the two centres, for analysis of the attending rheumatologist as potential predictor, centre is not taken into account as stratifier.

Leflunomide survival

Of the 279 patients included, 173 patients (62.0%) were withdrawn from leflunomide therapy, a withdrawal rate of 54.3 per 100 patient years. Seventeen patients were lost to follow-up. Figure 1 shows the Kaplan-Meier cumulative survival curve for all included patients. Figure 2 shows the Kaplan-Meier cumulative survival curves per centre. No significant differences in survival rates between both centres were found (p=0.20).

Figure 1. Kaplan-Meier estimate for withdrawal from leflunomide.



Legend: + = censored observation

Predictors for longer leflunomide drug survival

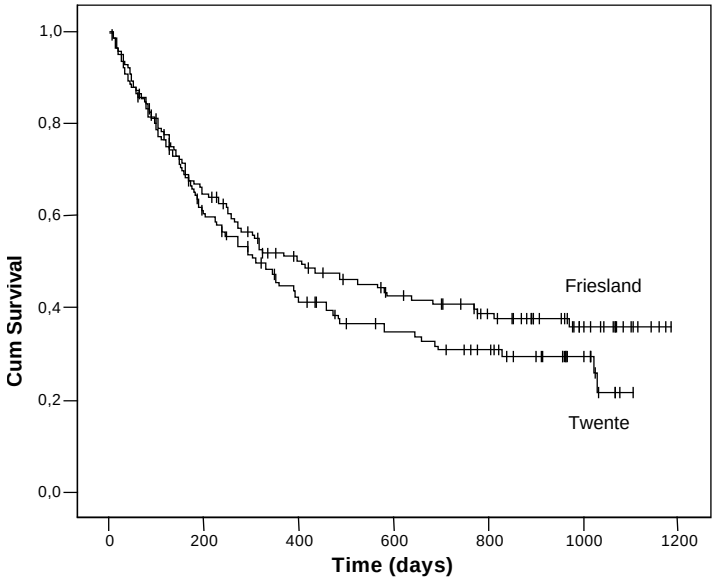
Independence of variables

Since the characteristics of the population treated per rheumatologist may differ, the association between rheumatologist and patient age, ESR at start of leflunomide, CRP at start of leflunomide, duration of RA or number of DMARDs prior to leflunomide were studied. Rheumatologist was found to be associated with disease duration ($p=0.01$) and number of previous DMARDs ($p<0.001$).

Rheumatoid factor status was not associated with systemic corticosteroid use at the start of leflunomide therapy.

Systemic corticosteroid use was not associated with ESR at start ($p=0.08$) and IgM rheumatoid factor status ($p=0.44$). However, significant positive associations were found between systemic corticosteroid use and CRP at start ($p<0.001$, mean CRP at start with and without concomitant corticosteroids was 48 and 30 mg/L, respectively).

Figure 2. Kaplan-Meier estimates for withdrawal from leflunomide per centre.



Legend: + = censored observation

Uni- and multivariate analysis

Gender, age, disease duration, IgM rheumatoid factor status, the number of previous DMARDs, serum creatinine, ESR and CRP at start of leflunomide were found not to be predictive for leflunomide survival.

However, concomitant systemic corticosteroid use at the start of leflunomide, and ESR at start of leflunomide (dichotomous; <35 versus ≥ 35 mm/hr) were recognized as predicting variables for leflunomide survival (Table 2). Patients with concomitant systemic corticosteroid use at start of leflunomide showed better leflunomide survival (Hazard ratio 95% [95CI] 1.35 [1.00-1.83]) compared with patients without concomitant systemic corticosteroids. Patients with ESR < 35 mm/hr at start of leflunomide showed better leflunomide survival at complete follow-up (Hazard ratio [95CI] 1.38 [1.01-1.88]) compared with patients with ESR ≥ 35 mm/hr. The attending rheumatologist was associated with leflunomide drug survival. From all rheumatologist, the rheumatologist with the median number of included patients was used as the reference rheumatologist for calculating maximal contrasts within the group of attending rheumatologists in this study.

Table 2. Univariate analysis for predictors for longer leflunomide drug survival.

Factor		*Univariate analysis*		*Multivariate analysis*	
		p-value	*Hazard ratio (95CI)*	*p-value*	*Hazard ratio (95CI)*
Concomitant systemic corticosteroids		0.05		0.006	
	No		1 (reference)		1 (reference)
	Yes		1.35 [1.00-1.83]		1.58 [1.14-2.21]
ESR start (mm/hr)		0.04		0.03	
	≥35		1 (reference)		1 (reference)
	<35		1.38 [1.01-1.88]		1.42 [1.03-1.96]
Rheumatologist		0.095	0.60-2.66[1]	0.02	0.54-2.30[1]

Legend: 95CI = 95% confidence interval, ESR start = erythrocyte sedimentation rate at the start of leflunomide therapy.

[1] Maximal contrasts between rheumatologists.

Multivariate analysis showed attending rheumatologist, concomitant systemic corticosteroid use and an ESR < 35 mm/hr at start of leflunomide to be related to leflunomide survival (Table 2).

Discussion

Predicting which patients will benefit from leflunomide is a challenge in optimising leflunomide treatment. Our data show that attending rheumatologist, concomitant systemic corticosteroid use and ESR at the start of leflunomide treatment to be predictors for survival of leflunomide in an outpatient population with RA in the setting of care-as-usual.

At the time we started our study no information on the predictors for longer survival of leflunomide was published. Wolfe et al [5], defining treatment failure as a combination of withdrawal or addition of a second DMARD, recognized adverse effects and clinical status prior to starting methotrexate or leflunomide as predictors for treatment failure. For obvious

reasons adverse events occurring during treatment were not part of our analysis. Contrary to Wolfe et al. [5] corticosteroid use was found to be of predictive value.

Wolfe et al report the exclusive use of self-reported data and the absence of laboratory data to predict discontinuation as one of the limitations of their study. In our study we used laboratory data as far as they are part of routine rheumatological care. Lower ESR, in contrast to CRP, was found to be a significant predictor of leflunomide survival.

Our data suggest that the individual rheumatologist influences leflunomide survival significantly. A recent publication on the long term survival of methotrexate also concluded that attending rheumatologist was a predictor for long term methotrexate survival [8]. Our findings are in accordance with this result and again suggest that remarkable heterogeneity exists in the treatment strategies of individual rheumatologists. Although the prescription of leflunomide was not prospectively standardised in our study, leflunomide was not considered the option of first choice in the study period. Clinical guidelines aim to reduce variations in practice and to promote uniform and consistent best practice. Whether development of guidelines on the application of leflunomide in RA will lead to more uniform strategies and improvement of treatment outcomes remains to be determined.

Siva et al. [7] found age < 44 or > 75 years, annual family income < $60.000 and the use of a 3-day 100-mg loading dose to be predictive for leflunomide discontinuation. In our study age was not found to be predictive. Annual income is not part of routine rheumatological care in our practices and therefore could not be scored in our study. Since all but three patients in our study started leflunomide using the dosing schedule advised in the Summary of Product Characteristics, the absence of a loading dose could not be recognized as a predictor in our study.

In this study a limited dataset was collected. Therefore, some predictors for leflunomide survival may have been missed in the current analysis. Retrospective data collection may have introduced a bias and therefore may have influenced results. However, no patients were excluded from the study, the dataset was complete and the data collected were not subject to observer bias. This suggests that if any bias was present this may have had only a limited influence.

Conclusion

Concomitant systemic corticosteroid use, ESR at the start of treatment and attending rheumatologist were found to be predictive for leflunomide survival. Whether specific interventions based on this information, for example by more frequent follow-up of patients with a higher risk of treatment withdrawal, will lead to improved treatment outcomes remains to be studied.

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Chapter 3

Therapeutic drug monitoring of A77 1726

Chapter 3.1

A rapid and simple determination of A77 1726 in human serum by high-performance liquid chromatography and its application for optimization of leflunomide therapy.

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Abstract

Objectives

Leflunomide is a disease-modifying antirheumatic drug, which is bioactivated by formation of A77 1726. In this study a rapid and simple quantitative assay using a reversed phase HPLC-UV method is validated for detection of A77 1726 in human serum.

Methods

The HPLC-UV method uses a mobile phase consisting of methanol and a KH_2PO_4-buffer (45mM, pH=3) (50:50,v/v), at a flow rate of 1 mL/min. A77 1726 is detected by UV-absorption at 295 nm with a retention time of 8.9 minutes. Demoxepam is used as internal standard.

Results

Validation showed lower and upper limits of quantitation of 0.5 and 100 mg/L, respectively. The assay was linear over the concentration range of 0.5-100 mg/L (r^2 > 0.999). Intra- and inter-day precision showed coefficients of variation within 15% over the complete concentration range; accuracy was within 8%. Commonly prescribed drugs to treat rheumatoid arthritis, like disease-modifying antirheumatic drugs, analgesics and corticosteroids, and their main metabolites, are separated from A77 1726 with a resolution > 2. Serum levels of A77 1726 in 37 patients on leflunomide therapy were determined using this HPLC-UV method. Measured serum A77 1726 serum concentrations in patient samples showed large variability with a range of 3 to 176 mg/L.

Conclusion

We developed an easy-to-operate and validated HPLC-UV method for determination of A77 1726, the active metabolite of leflunomide, in human serum. The proposed method can be employed for the assay of A77 1726 in rheumatoid arthritis patient samples.

Introduction

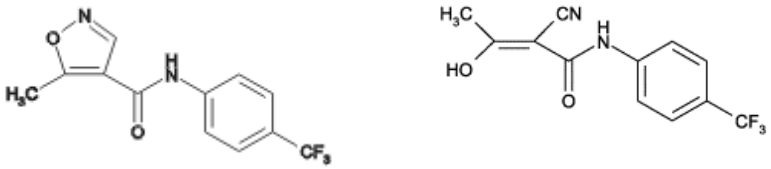
Leflunomide is a disease-modifying antirheumatic drug (DMARD) of the isoxazole class. After oral administration leflunomide is rapidly, non-enzymatically and completely converted into its long-acting, active metabolite A77 1726 (2-cyano-3-hydroxy-N-(4-trifluoromethylphenyl)-crotonamide; Figure 1) [1]. A77 1726 has antirheumatic activity through inhibition of the enzyme dihydro-orotate dehydrogenase (DHODH), a key enzyme in the *de novo* production of pyrimidines in T-lymphocytes, a process essential for T-lymphocyte proliferation.

Leflunomide showed antirheumatic activity which is comparable to methotrexate and sulfasalazine in randomized controlled trials using an oral dosage regimen starting with 100 mg once daily for three days followed by a maintenance dose of 20 mg once daily [2]. Overall in these trials 50-67% of patients reach efficacy end points during 12 month follow-up, with some patients reaching clinical efficacy 4-6 months after start of leflunomide therapy. Adverse events most frequently reported are gastrointestinal complaints (diarrhea, abdominal pain). The combination of late onset of efficacy, the high incidence of adverse events early in therapy and the uniform dosing schedule limit drug survival rates of leflunomide in populations with rheumatoid arthritis [3-5]. On the basis of these results optimization of leflunomide therapy is needed.

An option for treatment optimization is dose adjustment on the basis of A77 1726 steady state serum concentrations. In preregistration pharmacokinetic population modelling studies, a relationship between steady state A77 1726 serum concentrations and the probability of clinical success is suggested [6]. Leflunomide is rapidly and completely metabolized after oral administration, for that reason serum concentrations are unmeasurable. Furthermore, no clinically relevant inhibition of DHODH by leflunomide is supposed, leaving the antirheumatic activity of leflunomide negligible. Therapeutic drug monitoring therefore should focus on the major active metabolite A77 1726.

Earlier, published methods for determination of A77 1726 had several drawbacks. For example these methods lack information on interference of detection and quantitation of the analyte, A77 1726, by co-medication frequently used in patients with rheumatoid arthritis [7]; did not consider hydrolysis of leflunomide in extraction solvents containing potassium carbonate [8]; or had a upper limit of quantitation (due to loss of linearity) that did not cover the complete concentration range expected to be obtained in patient samples [9,10].

Figure 1. Chemical structures of leflunomide (left; CAS 75706-12-6) and its major metabolite A77 1726 (right; 108605-62-5).



Moreover, information on the stability of A77 1726 in serum kept under refrigerated conditions for more than one month [7] was lacking.

To study the potential value of therapeutic drug monitoring of A77 1726 in optimizing the treatment schedule a validated method of analysis in human serum is needed. In this study we present a rapid and simple, validated HPLC-UV method for A77 1726 in human serum. Moreover, data are presented on the range of steady state serum concentrations of A77 1726 in a population of patients with rheumatoid arthritis on 10 to 20 mg leflunomide daily.

Material and methods

Equipment

Chromatographic separation was performed using a Waters HPLC apparatus (Milford, MA, U.S.A.) consisting of a gradient pump and a column heater (model 2690) and a variable wavelength detector (model 996 PAD). Isocratic chromatographic separation was performed on a reversed-phase LiChrospher 100 RP-18e column (5 µm; 125 x 4 mm; Merck (Darmstadt, Germany)). The column temperature was maintained at 25°C.

All samples and standard solutions were chromatographed using a mixture of methanol: KH_2PO_4 (45 mM, pH=3) (50:50, v/v) as the mobile phase (flow rate 1.0 mL min^{-1}), and UV-detection at 295 nm and an injection volume of 20 µL. Data from each chromatographic run were processed using Waters Millennium 32 software. Concentrations were calculated from the peak height ratios in relation to the internal standard.

Preparation of the mobile phase

The mobile phase (methanol: KH_2PO_4 (45 mM, pH=3) (50:50, v/v)) was prepared by adding methanol and the KH_2PO_4-buffer and mixing well. The KH_2PO_4-buffer (45 mM, pH=3) was prepared by dissolving 6.124 g KH_2PO_4 in 1000 mL distilled water and correcting the pH to 3 with phosphoric acid 85%. The mobile phase was daily degassed and filtered before use.

Chemicals

Acetonitrile and methanol were purchased from Labscan Ltd (Dublin, Ireland). Ethanol, KH_2PO_4, demoxepam and phosphoric acid 85% were obtained from Merck (Darmstadt, Germany). Acetaminophen, azathioprine, celecoxib, diclofenac, hydroxychloroquine, ibuprofen, methotrexate, naproxen, rofecoxib, prednisolone, sulfapyridine, sulfasalazine, 5-aminosalicylic acid, 6-mercaptopurine were purchased from Bufa (Uitgeest, The Netherlands). Leflunomide and A77 1726 were kindly provided by Aventis Pharma (Hoevelaken, The Netherlands). Human serum was derived from a pool of anonymous and unpaid, healthy volunteers.

Preparation of standard solutions and samples

For preparation of the stock standard solution, A77 1726 was dissolved in ethanol at a concentration of 1 mg/mL, placed in an ultrasonic water bath for 1 hour and subsequently diluted to 100, 10 and 1 mg/L by spiking blanc human serum.

For the stock internal standard solution, demoxepam was dissolved at a concentration of 2.5 mg/L in acetonitrile.

Patient serum samples were prepared by adding 1.0 mL internal standard solution to 100 µL serum. The tubes were capped, vortexed for 3 seconds and centrifuged at 3000 rpm for 5 minutes. Two-hundred µL of the supernatant was transferred into a glass tube and evaporated to dryness under a gentle nitrogen stream at 40 °C. The residue was dissolved in 200 µL of the mobile phase. The reconstituted specimens were vortexed for 10 seconds and analysed with HPLC-UV.

Serum calibration standards (0.5, 1, 10, 25, 50, and 100 mg/L) and quality control standards were separately prepared by spiking blanc pooled human serum with increasing amounts of A77 1726 stock standard solution and further processed as patient serum samples.

Validation

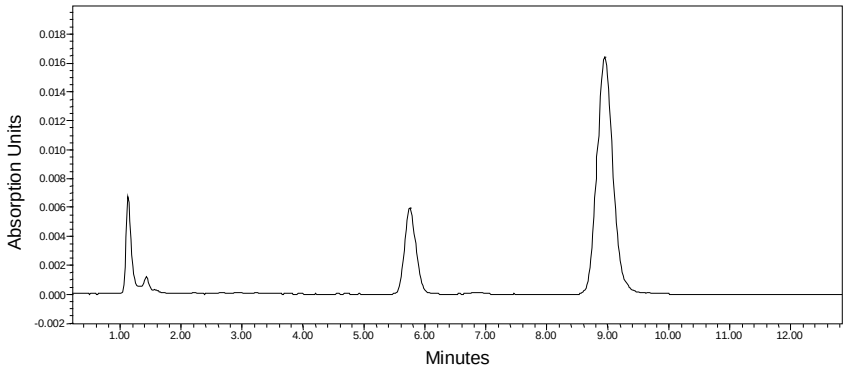
Linearity was examined over the complete concentration range of A77 1726 (0.5-100 mg/L) and using acceptable fit to linear regression by calculating regression coefficients and evaluation of sum of squares of residuals, tested with analysis of variance.

Selectivity was examined by studying the interference of endogenous peaks and antirheumatic medication with the determination of A77 1726 and the internal standard. Criteria set for lack of interference were a resolution between the peak of A77 1726/internal standard and potentially interfering medication of > 2. Selection of potentially interfering antirheumatic drugs was based on UV-absorption spectra at 295 nm. These drugs were studied at serum concentrations reached with doses routinely used for rheumatoid arthritis. Drugs and their major metabolites studied were non-steroidal anti-inflammatory drugs (celecoxib, diclofenac, ibuprofen, naproxen, rofecoxib), DMARDs (azathioprine/6-mercaptopurine, hydroxychloroquine, methotrexate, sulfapyridine, and sulfasalazine/5-aminosalicylic acid) and acetaminophen. Since (methyl)prednisolone and prednisone do not have relevant absorption at 295 nm, these compounds are very unlikely to interfere with detection and quantitation of A77 1726. However, to confirm this, the major metabolite of prednisone, prednisolone, was studied for interference.

The intra-day reproducibility was examined by analysing five independent preparations of each standard concentration, each injected twice, on the same day. Inter-day reproducibility was examined by analysing five independent preparations of each concentration, each injected twice, on three different days within a period of two weeks. For each day freshly prepared standard solutions were made. All standard solutions were prepared from an independent standard stock solution. The calibration curve used for calculating patient samples was the calibration curve determined from all data of the five separate repetitions of intra-day reproducibility testing. These data were fitted using least sum of squares analysis. Criteria for acceptance for each separate calibration curve were a regression coefficient of > 0.99 and a back-calculated concentration within 15% of the respective target concentrations.

Stability of A77 1726 40 mg/L in human serum was studied by repeated, duplicate analysis. The solution was divided into 5 mL aliquots and kept frozen at -20 ºC until the moment of analysis. Samples were analysed at 0, 1, 2, 4 weeks and every 4 weeks for a period of 5 months, subsequently. Criteria for acceptable stability were differences between the baseline concentration and the concentration at follow-up < 5%.

Figure 2. Chromatogram of serum of a patient with a A77 1726 serum concentration of 32 mg/L (retention times of demoxepam (internal standard) and A77 1726, 5.8 and 8.9 minutes, respectively).



Patient samples

All consecutive patients visiting our outpatient department of rheumatology from January to October 2003, who were on stable, daily doses of leflunomide for at least 6 months were asked to participate in this part of the study. After obtaining written informed consent a single venous blood sample in anti-coagulant-free evacuated containers was taken for determination of A77 1726. After sampling, blood was directly centrifuged and serum was kept frozen at –20 ºC. Directly prior to analysis samples were processed as described above. In case of serum concentrations of A77 1726 above the upper limit of quantification, samples were diluted 1:1 with blanc human serum and re-analysed. All patient samples were injected twice, comparable to standard and control samples.

The Medical Ethical Committee approved the study.

Results

Method validation

With the described method resolution >2 of A77 1726 and the internal standard (demoxepam) was achieved (Figure 2). The retention times of demoxepam and A77 1726 are 5.8 and 8.9 minutes, respectively.

Table 1. Intra- and inter-day reproducibility for A77 1726 in human serum.

	A77 1726 intra- day reproducibility[1]			*A77 1726 inter-day reproducibility* [2]		
Spiked (mg/L)	*Measured (mg/L)*	*CV (%)*	*Accuracy (%)*	*Measured (mg/L)*	*CV (%) (mg/L)*	*Accuracy (%)*
0.5	0.52 ± 0.03	8.1	4.4	0.53 ± 0.03	5.0	7.0
1	1.08 ± 0.03	2.8	8.0	0.94 ± 0.12	13.2	-5.9
10	9.95 ± 0.06	0.6	-0.5	10.03 ± 0.30	3.0	0.3
25	24.5 ± 0.05	0.2	-1.9	24.6 ± 0.52	2.1	-1.8
50	48.0 ± 0.03	0.1	-3.9	48.4 ± 0.73	1.5	-3.2
100	100.2 ± 0.15	0.1	0.2	100.7 ± 0.61	0.6	0.7

Legend: CV = coefficient of variation; [1] From 5 repetitions each; [2] Three separate days, 5 repetitions each day.

Chromatograms displayed no interference of endogenous peaks in spiked blanc human serum samples and patient samples. No interference of antirheumatic medication with peaks of demoxepam and leflunomide was detected, with all co-medication peaks having a resolution > 2 compared with the peaks of A77 1726 or the internal standard.

The calibration curve for A77 1726 was linear over the full concentration range from 0.5 mg/L to 100 mg/L, with a correlation coefficient of 0.9996. Correlation between the ratio as calculated from the chromatograms and the spiked concentrations is best described by:

[Concentration A77 1726] (mg/L) = 11.5 x [peak height ratio] + 0.14

Table 1 shows the results of the intra- and inter-day reproducibility, respectively. Coefficients of variation and accuracy for intra- and inter-day reproducibility are within 15% over the concentration range from 0.5 to 100 mg/L. On the basis of these results, the lower and upper limits of quantitation for A77 1726 with this analytical method are 0.5 mg/L and 100 mg/L respectively.

Results from the assays for studying stability of A77 1726 over the period of 5 months are shown in table 2. Until week 8 samples show acceptable stability, with differences between the baseline concentration and concentration at follow-up < 5%.

Table 2. Stability of A77 1726 40 mg/L in human serum.

T (weeks)	*Measured concentration (mg/L; n=2 each)*	*Deviation from T=0 (mg/L)*	*Devation from T=0 (%)*
0	40.7	-	-
1	41.7	1.0	2.4
2	42.6	1.9	4.7
4	42.1	1.4	3.4
8	40.9	0.2	0.5
13	43.9	3.2	7.9
17	41.3	0.6	1.5
22	38.2	-2.5	-6.1

Patient samples

Thirty-seven blood samples were taken for determination of A77 1726 concentrations. Patient and treatment characteristics of the population are given in Table 3. Measured serum concentrations show large variability, ranging from 3 to 176 mg/L. For two patients (5%) A77 1726 serum concentrations were found to be > 100 mg/L, 133 and 176 mg/L, respectively. Mean[SD] concentrations for the 10 and 20 mg daily dose groups are 39[30] and 42[37] mg/L, respectively.

Discussion

The current analytical method shows acceptable intra- and inter-day accuracy and precision over the A77 1726 concentration range from 0.5-100 mg/L. Endogenous serum peaks and antirheumatic medication did not interfere with the detection of A77 1726 in the current HPLC-UV method. Stability of A77 1726 in human serum kept frozen at –20 °C until the moment of analysis is shown up till 8 weeks after sampling. This enables analysing patient samples in one run up to 8 weeks after sampling in future studies.

To study the applicability of the validated method in clinical practice a series of patient serum samples were analysed for A77 1726 concentrations. The serum concentrations are

Table 3. Patients characteristics for population included for determination of A77 1726 concentrations[1].

Characteristics	
Number of patients	37
Age (years)	70 [12]
Duration of RA (years)	12 [10]
Rheumatoid factor positive (%)	76
Leflunomide prescribed as first DMARD (%)	16
Number of DMARDs prior to leflunomide	2.0 [1.6]
Duration of leflunomide use (days)	970 [237]
Range	214-1281
Prescibed daily leflunomide dose (mg)	
10	8
15 (alternating 10 and 20 mg)	2
20	27

Legend: DMARD = disease-modifying antirheumatic drug; RA= rheumatoid arthritis. [1] Values are means [SD] unless stated otherwise;

characterized by large interindividual variation. The validated concentration range covers 95% of the concentration found in the patient samples in our study.

As stated, previously published methods for determination of A77 1726 had several drawbacks concerning lack of information on interference of detection and quantitation of the analyte, A77 1726, by antirheumatic co-medication [7]; did not consider hydrolysis of leflunomide in extraction solvents containing potassium carbonate [8]; or had an upper limit of quantitation (due to loss of linearity) that did not cover the complete concentration range expected to be obtained in patient samples [9,10]. Moreover, information on the stability of A77 1726 in serum kept under refrigerated conditions for more than one month [7] was lacking. The HPLC-UV method described here, focuses on A77 1726 as the only analyte of interest, is validated for the absence of interference of other, commonly prescribed

antirheumatic medication on the determination of A77 1726 and studies stability of A77 1726 in serum for a period up till 5 months.

A77 1726 is the metabolite responsible for inhibition of DHODH and therefore antirheumatic activity. Moreover, reports on pharmacokinetics of leflunomide show that no detectable serum levels of leflunomide are reached in dose regimens for rheumatoid arthritis [1]. A77 1726 itself is excreted in faeces or metabolised further to 4-trifluoromethylaniline oxalinic acid [1]. The role of leflunomide and the metabolites of A77 1726 in antirheumatic activity are currently not clear and systemic exposure to these metabolites is minimal [1]. Therefore, quantitative assays for use in patient samples should focus on A77 1726 as the analyte of interest.

A proportion of the patients with rheumatoid arthritis will be treated with combinations of DMARDs, analgesics and/or corticosteroids, within the current treatment paradigm of rheumatoid arthritis. Therefore, interference of concomitant medication with the quantitation of A77 1726 is of special interest in the patient group treated with leflunomide. Our method is validated for absence of interference of concomitantly prescribed antirheumatic drugs and their main metabolites on the quantitation of A77 1726.

Conclusion

We developed an easy-to-operate and validated HPLC-UV method for determination of A77 1726, the active metabolite of leflunomide, in human serum. The proposed method can be employed for the assay of A77 1726 in rheumatoid arthritis patient samples.

Acknowledgements

We like to thank mr. R. Keuper for his work on the validation of the HPLC-UV method. Furthermore we like to thank the rheumatologists ms. P. Houtman MD PhD, G. Bruijn MD PhD and E. Griep MD PhD for their work on collecting the patient samples.

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Chapter 3.2

Therapeutic drug monitoring of A77 1726, the active metabolite of leflunomide.

Serum concentrations predict response to therapy in patients with rheumatoid arthritis.

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Ann Rheum Dis (in press).

Abstract

Objectives

Leflunomide is the prodrug of the disease-modifying antirheumatic metabolite A77 1726. Over 50% of patients withdraw from leflunomide therapy within 1 year after start of treatment, mainly because of adverse drug reactions. Therapeutic drug monitoring of A77 1726 may be useful to predict effectiveness of leflunomide treatment. We have studied the relationship between A77 1726 steady state serum concentrations and disease activity using 28 joints (DAS_{28}), respectively DAS_{28} response.

Methods

Outpatients with rheumatoid arthritis on a stable leflunomide dose > 4 months were included. DAS_{28} parameters and adverse drug reactions were registered. Blood samples were drawn for determination of the A77 1726 concentration.

Results

In fifty-two patients A77 1726 serum concentrations were determined. Concerning the primary end point, the relation of A77 1726 serum concentrations with DAS_{28}-response category, the Receiver Operating Characteristics (ROC) curve shows an area under the curve (AUC) of 0.73 (95% confidence interval (CI95) 0.54-0.93; $p<0.05$), sensitivity exceeding 99% at concentrations below 16 mg/L. Concerning the secondary end point, DAS_{28} values at the moment of sampling show no relationship between A77 1726 concentrations, with AUC of the ROC-curve 0.50 (CI95 0.33-0.67; NS).

Conclusions

A77 1726 steady state serum concentrations show a relationship with DAS_{28} response. Determination of A77 1726 serum concentrations for patients with insufficient response to therapy may offer clinically relevant information for decisions on treatment continuation or dose adjustment.

Introduction

Leflunomide is a disease-modifying antirheumatic drug (DMARD) of the isoxazole class. After oral administration leflunomide is rapidly, non-enzymatically and completely converted into its active metabolite A77 1726 (2-cyano-3-hydroxy-N-(4-trifluoromethylphenyl)-crotonamide) [1]. A77 1726 has antirheumatic activity through inhibition of the enzyme dihydro-orotate dehydrogenase (DHODH). DHODH is a key enzyme in the *de novo* production of pyrimidines in T-lymphocytes, a process essential for T-lymphocyte proliferation. A77 1726 has a long mean plasma half life of 15.7 days (range 14-18 days) in patients with rheumatoid arthritis [1-3].

Leflunomide has antirheumatic activity comparable with methotrexate and sulfasalazine [4]. Although an antirheumatic effect can be observed within a few weeks, in some patients onset of effectiveness takes up to 6 months [5]. Moreover, a high incidence of adverse events, possibly explained by the uniform dosing schedule with only few options for dose adjustments, is noted. These factors limit drug survival rates and effectiveness of leflunomide in populations with rheumatoid arthritis [6-8]. Therefore, optimization of leflunomide treatment is warranted.

Therapeutic drug monitoring based on A77 1726 steady state serum concentrations may allow individualised dose adjustment and consequently increase clinical effectiveness. In phase II pharmacokinetic population modelling studies, a relationship between steady state A77 1726 serum concentrations < 13 mg/L and a reduced probability of clinical success is described [9].

In this study we investigated the relationship between rheumatoid arthritis disease activity and the steady state serum concentrations of A77 1726 in patients treated with leflunomide.

Methods

Patients

Patients with rheumatoid arthritis, visiting the outpatient department of rheumatology from the 4 participating centres in the period of January 2003 to January 2004, who were on fixed, doses of leflunomide for at least 4 months were asked to participate. After obtaining

written informed consent a single venous blood sample was taken for determination of A77 1726. Further, patient-, rheumatoid arthritis- and medication-characteristics and the 4 parameters for calculation of the Disease Activity Score using 28-joint counts (DAS_{28}) were recorded; tender and swollen joint counts, erythrocyte sedimentation rate and a 100 mm visual analogue scale for general health status as estimated by the patient. Further, DAS_{28} at the time of starting of leflunomide was retrieved from the patients record. All DAS_{28} parameters were scored for every patient by the same rheumatologist at every visit. DAS_{28} was calculated from the four parameters at the end of the study to prevent influence of the DAS_{28}-value on treatment decisions.

Exclusion criteria were participation in another study, concomitant use of daily doses of >10 mg prednisone-equivalents or pharmacokinetically interacting medication. Interacting drugs were detected by checking medication histories for the prescription of rifampicin, activated charcoal and cholestyramine [3].

Since non-compliance to leflunomide therapy influences exposure to leflunomide and therefore steady state serum concentrations of A77 1726, an effort was made to gain insight into therapy compliance. For this purpose the local pharmacies of the patients were asked for leflunomide-refill data. Tracking of virtually complete prescription data is possible since in The Netherlands patients usually register with one pharmacy only and local pharmacies keep a computerised, detailed record of all delivered prescriptions. From the refill data the refill rate is calculated:

$$\text{Refill rate} = \frac{(\text{number of tablets delivered/number of days since leflunomide start})}{\text{number of prescribed tablets per day}}$$

Refill rates under 1.0 represent underconsumption, above 1.0 overconsumption. Refill rates from 0.9-1.1 were categorised as good compliance [10].

The human medical-ethics research committee approved the study.

Determination of A77 1726

Blood samples were analysed for A77 1726 by means of a validated high-pressure liquid chromatography method [11]. Mean [SD] A77 1726 serum concentration and the percentage of patients with a steady state A77 1726 serum concentration < 13 mg/L, the previously reported cut-off A77 1726 concentration for optimal clinical success [9], were calculated.

End points

The primary end point was to determine the relationship between A77 1726 serum concentration and the DAS_{28}-responder category. DAS_{28}-responder category was determined comparing the DAS_{28} at the start of leflunomide therapy with DAS_{28} at the moment of sampling. Responders were categorised according to EULAR criteria [12,13]. Since in clinical rheumatological practice moderate response is insufficient as a goal for therapy, for analysis the comparison of good versus moderate or non responders was made. The null hypothesis for this end point was that low A77 1726 serum concentrations will predict poorer response. All patients for whom the A77 1726 serum concentration, DAS_{28} at the start of leflunomide therapy and DAS_{28} at the moment of sampling were recorded, were included for determination of this end point. Since disease activity is directly influenced by concomitant use of DMARDs, patients on leflunomide in combination with other DMARDs were excluded from this analysis.

The secondary end point was to determine the relationship between A77 1726 serum concentration and disease activity at the moment of sampling. DAS_{28} was categorised in low ($\leq$3.2) or high (>3.2) disease activity, according to EULAR criteria [12,13]. The null hypothesis for this end point was that lower A77 1726 serum concentrations are associated with high disease activity. All patients for whom the A77 1726 serum concentration and DAS_{28} at the moment of sampling were recorded, were included for analysis. As for the primary end point concomitant use of DMARDs other than leflunomide was an exclusion criterion for this analysis.

Statistical analysis

SPSS 12.0.1 for Windows was used for data collection, data validation, data selection, and statistical analysis. Normality of the distribution of A77 1726 serum concentrations per dose group is tested according to Kolmogorov-Smirnov. Differences in mean A77 1726 serum concentrations between the leflunomide dose groups are studied using Students t-test. Receiver operator characteristics (ROC) curves and chi-square analysis were used to determine the relationship of A77 1726 serum concentrations with disease activity and DAS_{28} responder category, respectively. The relationship between disease activity or response and corticosteroid- or NSAID-use was tested using chi-square analysis.

Table 1. Demographic and clinical characteristics.[1]

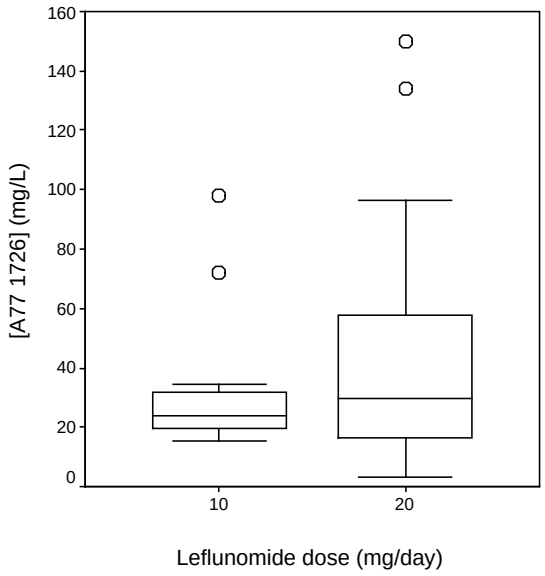
Characteristics	
Number of patients	52
Age (years)	69 [12]
Female (%)	67
Period since diagnosis of rheumatoid arthritis (years)	11 [10]
Rheumatoid factor positive (%)	71
Leflunomide prescribed as first DMARD (%)	21
DMARDs prior to leflunomide (n)	2.0 [1.7]
Range	0-6
Duration of leflunomide use (days)	921 [299]
Range	136-1327
Patients > 1 year of leflunomide therapy	90%
Patients > 2 year of leflunomide therapy	60%
Prescribed daily leflunomide dose (%)	
10 mg	25
20 mg	65
other[2]	10
Concomitant corticosteroid use (%)	44
Concomitant other DMARD use (%)	8
Concomitant NSAID use[3] (%)	58

Legend: DMARD = disease-modifying antirheumatic drug, NSAID = non-steroidal anti-inflammatory drug. [1]Mean [standard deviation] unless stated otherwise. [2]Range 5-15 mg leflunomide daily. [3]At least one active prescription at the moment of sampling, low-dose (<100 mg daily) salicylates not included.

Results

In 52 patients the A77 1726 steady state concentration was determined (Table 1). A77 1726 steady state concentrations showed large inter-individual variability, with concentrations ranging from 3 to 150 mg/L (Figure 1). In 6 patients (12%) A77 1726 concentrations were < 13 mg/L, all on daily leflunomide doses of 20 mg.

Figure 1. Box-whisker plots for A77 1726 serum concentrations for 10 and 20 mg leflunomide daily dose.



Legend: o = outlying value.

In 2 patients A77 1726 plasma concentrations exceeded 100 mg/L, with both patients on 20 mg leflunomide daily. Mean [SD] A77 1726 serum concentrations in the 10 and 20 mg dose were 33[24] (range 15-98) and 42[35] (range 3-150) mg/L, respectively. The mean A77 1726 serum concentrations in each dose group tended to differ although statistical significance was not reached (p=0.12).

Seventy-one percent of the patients showed compliance with refill rates between 0.9 and 1.1. Refill rates varied between 0.56 and 1.35, with 22% of the population having a refill rate lower than 0.9 and 7% of the population having a refill rate above 1.1. Refill rate and A77 1726 serum concentration were not correlated ($r < 0.008$). Patients with A77 1726 concentrations < 13 mg/L or > 100 mg/L showed compliance with refill rates between 0.93 and 1.06.

Table 2. Demographic and clinical characteristics (population for the analysis of DAS_{28} response).[1]

Characteristics	
Number of patients	25
Age (years)	68 [13]
Female (%)	72
Period since diagnosis of rheumatoid arthritis (years)	8[7]
Rheumatoid factor positive (%)	60
DAS_{28} at baseline	5.1[0.9]
DAS_{28} > 5.1 (n)	13
DAS_{28} > 3.2 -≤ 5.1 (n)	12
Leflunomide prescribed as first DMARD (%)	24
Concomitant corticosteroid use (%)	40
Concomitant other DMARD use (%)	0
Concomitant NSAID use[2] (%)	38

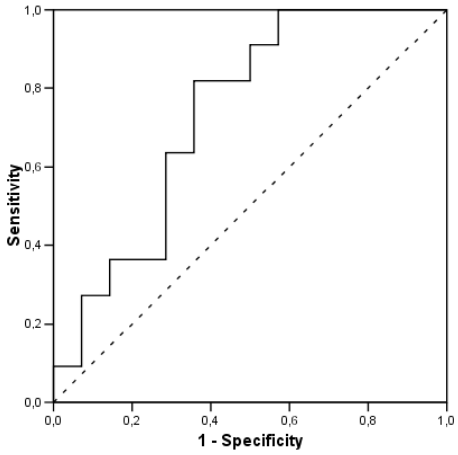
Legend: DAS_{28} = disease activity using 28-joint counts, DMARD = disease-modifying antirheumatic drug, NSAID = non-steroidal anti-inflammatory drug. [1]Mean [standard deviation] unless stated otherwise. [2]At least one active prescription at the moment of sampling, low-dose (<100 mg daily) salicylates not included.

Primary end point: DAS_{28}-response versus A77 1726 concentration

In 25 patients DAS_{28} values at the start of leflunomide treatment and at the moment of sampling were recorded (Table 2). Figure 2 shows the ROC-curve for DAS_{28} response in relation to the A77 1726 concentration. The area under the curve is 0.73 (CI95 0.54-0.93; $p<0.05$). Sensitivity is 90,9% at the 18 mg/L A77 1726 concentration level. At the 16 mg/L level sensitivity is 100%; that is, patients with good response, according to EULAR criteria, are not recorded below this A77 1726 serum concentration.

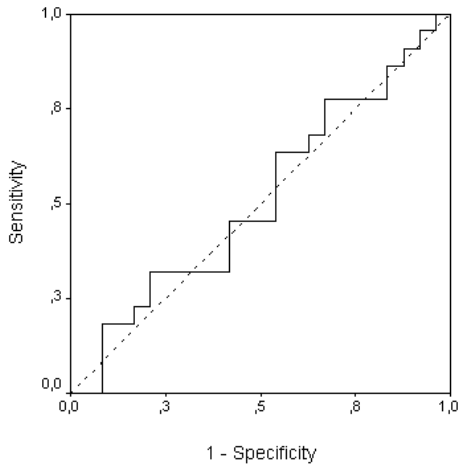
Table 3 shows the 2x2 table for test results (positive test: A77 1726 serum concentration ≥16 mg/L) versus response (positive response: good responder according to DAS_{28} criteria). Chi-square analysis shows a significant dependence of DAS_{28}-response and A77 1726 plasma concentration using 16 mg/L as cut-off point for the dichotomy ($p=0.02$).

Figure 2. ROC-curve for DAS_{28} -response versus A77 1726 concentration (AUC 0.73 (CI95 0.54-0.93)).



Legend: ——— ROC-curve; - - - - - - Reference line.

Figure 3. ROC-curve for DAS_{28} versus A77 1726 concentration (AUC 0.50 (CI95 0.33-0.67)).



Legend: ——— ROC-curve; - - - - - - Reference line.

Table 3. 2x2 table for response versus A77 1726 plasma concentration (n (%)).

		DAS_{28} response category		
		Good	*Non or moderate*	*Total*
A77 1726 plasma concentration	*≥16 mg/L*	10 (40%)[a]	8 (32%)[b]	18 (72%)
	<16 mg/L	0 (0%)[c]	7 (28%)[d]	7 (28%)
	Total	10 (40%)	15 (60%)	25 (100%)

Legend: [a-d] = notes for the calculation of the PPV, NPV and likelihood ratios.

PPV = positive predictive value = a/(a+b)

NPV = negative predictive value = d/(c+d)

Likelihood ratio for positive test result = (a/(a+c))/(b/(b+d))

Likelihood ratio for negative test result = (c/(a+c))/(d/((b+d))

The positive predictive value, a high A77 1726 serum concentration (≥ 16 mg/L) and response (good response according to DAS_{28} criteria) is 56% (CI95 33-79%); an A77 1726 serum concentration of ≥ 16 mg/L in 56% of the patients correctly predicts that they have responded well. The negative predictive value, a low A77 1726 serum concentration (<16 mg/L and 'no response') is 100% (CI95 not calculated since good responders were not recorded at A77 1726 serum concentrations < 16 mg/L); an A77 1726 serum concentration <16 mg/L is associated with non-response in each case were this low A77 1726 serum concentration is found. The likelihood ratio for a positive test result, i.e. the ratio of a positive test result (A77 1726 serum concentration ≥ 16 mg/L) for good versus moderate or non responders, is 1.9 (CI95 1.1-2.9). The likelihood ratio for a negative test result, i.e. the ratio of a negative test result (A77 1726 serum concentration < 16 mg/L) for good versus non- or moderate responders, is 0 (CI95 0.0-1.5).

DAS_{28}-response was not significantly related to corticosteroid- (p>0.1) nor NSAID-use (p>0.1).

Secondary end point: DAS_{28} versus A77 1726 concentration

Data from 45 patients, of the 52 patients included in the study, were used for this end point. Five patients were excluded because of combination therapy with a DMARD other than leflunomide (3x methotrexate, 2x hydroxychloroquine), 2 patients were excluded since no DAS_{28} could be calculated due to missing data ($VAS_{general\ health}$). Figure 3 shows the

ROC-curve for DAS_{28} in relation to the A77 1726 concentration. Area under the ROC-curve is 0.50 (95% confidence interval (CI95) 0.33-0.67; p>0.1). Disease activity was not significantly related to corticosteroid- (p=0.1) or NSAID-use (p>0.1).

Discussion

Although our data show no association between serum concentrations of A77 1726 and disease activity, none of the patients with low A77 1726 concentrations had a good response according to EULAR criteria.

Criteria for therapeutic drug monitoring

The International Association for Therapeutic Drug Monitoring and Clinical Toxicology defines therapeutic drug monitoring as '.. the measurement made in the laboratory of a parameter which, with appropriate interpretation, will directly influence prescribing procedures ..' [14]. Ensom et al [15] have defined criteria for drugs for which therapeutic drug monitoring may have additional value. These criteria are: the drug has to be part of the standard of care for the indication, the drug can be easily determined in biological matrices, the pharmacological effect of the drug is not directly measurable, the drug has a small therapeutic window, and the therapy with the drug has to be continued for a period long enough to be able to determine the effect of therapy adjustments based on therapeutic drug monitoring. Further, Ensom et al state that there has to be a large inter- or intra-individual variability in pharmacokinetics and that there has to be a relationship between drug concentration levels and clinical effectiveness. When translating these criteria into our data on leflunomide, therapeutic drug monitoring for leflunomide/A77 1726 may be an interesting option for improving effectiveness: leflunomide is one of the DMARD-options for long-term treatment of RA with dose-limiting toxicity, the effectiveness of leflunomide cannot be determined early after therapy initiation or dose adjustments, and A77 1726 serum concentration can be determined using a relatively simple chromatographic technique.

Concerning the last criterion mentioned by Ensom, the large variability of drug concentration levels, data from clinical studies are scarce. Large inter-individual variability of A77 1726 concentrations in a RA-population was shown in a recently published study, with A77 1726 concentrations varying from 5 to 93 mg/L (n=12) [16]. Large inter-individual variability of A77 1726 serum concentrations is also reported by Mladenovic et al [2]. Our

data correlate well with these results. It can be concluded that this criterion, as set by Ensom, is met for the leflunomide case.

It would be interesting to know whether the variability in A77 1726 concentrations can be reduced by individualised dosing, based on patient characteristics. However, one study on the influence of demographic variables found that none of the variables studied, affected A77 1726 steady state concentrations substantially [9]. This leaves the possibility of adjusting the leflunomide treatment regimen post hoc on the basis of therapeutic drug monitoring.

In 1997, based on data from phase I and II studies, a pharmacokinetic/ pharmacodynamic model for predicting therapeutically active serum concentrations of A77 1726 was published [9]. Using follow-up results after 6 months of leflunomide therapy and Paulus criteria as the efficacy end point, the authors conclude that the maximum probability of clinical success would be obtained by a dose rate which maintains the steady state A77 1726 serum concentration above 13 mg/L. On the basis of this model the authors state that a daily leflunomide dose of 20 mg would result in A77 1726 steady state concentrations above 13 mg/L in > 99% of the patients. However, our data show that 12% of the patients reach A77 1726 concentrations < 13 mg/L despite good therapy compliance, defined as pharmacy refill rates between 0.9 and 1.1. Using the previously reported model [9] we conclude that in a significant proportion of the RA-population, a daily leflunomide dose of 20 mg does not lead to steady state A77 1726 concentrations which are related with a maximum probability of clinical success.

On the other hand, our data support the conclusion [9] that a certain steady state concentration has to be exceeded in order to obtain clinical success. The target concentration was previously determined to be 13 mg/L [9], our results suggest a target concentration exceeding 18 mg/L for > 90% sensitivity or > 16 mg/L for >99% sensitivity. Twenty-eight percent of our patients have steady state A77 1726 plasma concentrations < 16 mg/L representing approximately 50% of the patients with inadequate response, that is non- or moderate responders according to EULAR-criteria.

Some remarks on the current study and the interpretation of the results have to be made.

Our study was retrospective in design and included a relatively small study population for study of the relationship between A77 1726 steady state serum concentrations and response. For this reason the results of our study necessitate confirmation in a larger, prospective study. Whether the current design and sample size has had an influence on the study findings, besides statistical power, is unclear. Some considerations point to the fact

that this may not be the case. Attending rheumatologists were not aware of the A77 1726 serum concentration at the moment of blood sampling and collecting parameters for calculation of the DAS_{28}, making bias in estimating disease activity less obvious. Further, as discussed earlier, our data are in accordance with the results of Weber et al [9]. Both studies found an A77 1726 serum concentration cut-off point for response to therapy and at approximately the same concentration level.

In our study 44% and 58% of the patients concomitantly used corticosteroids and NSAIDs, respectively. Since both corticosteroids and NSAIDs may influence individual DAS_{28}-parameters these concomitant medications may have influenced the results of our study. Although no relationship between corticosteroid- nor NSAID-use and disease activity or response was determined, our study was not designed to correct for this potential confounder.

No correlation between disease activity at the moment of sampling and A77 1726 serum concentrations was found. One possible explanation for this result is the fact that disease activity at the moment of sampling is not stratified for baseline disease activity. DAS_{28} responders categories which, besides disease activity at the moment of measurement, holds in it the change of disease activity from baseline as well, is an appropriate and validated end point for this analysis. In absence of published data on the potential, direct relationship between A77 1726 serum concentrations and disease activity we performed this analysis.

Furthermore, in our study no specific efforts were made to optimize patient compliance with leflunomide therapy, besides routinely exercising good clinical practice. Structural deviations in medication intake from the prescribed daily dose are likely to influence steady state A77 1726 serum concentrations. However, no influence on study results from deviations in therapy compliance, that is refill rates outside the range of 0.9-1.1, are expected for several reasons. Firstly, no correlation between refill rate and A77 1726 serum concentration over the complete concentration range was detected. Secondly, patients with A77 1726 serum concentrations <13 mg/L and > 100 mg/L all show refill rates between 0.93 and 1.06. Therefore, low or high refill rates also are not associated with A77 1726 serum concentrations in the lower or upper concentration ranges.

Clinical implications

Our data demonstrate that disease activity according to DAS_{28} criteria is not correlated with A77 1726 serum concentrations. When disease activity at baseline is taken into account one has a measure of response which enables an evaluation of leflunomide-induced DAS_{28}-

responder categories. Interestingly, our data on the relationship between A77 1726 concentrations and DAS_{28}-response reveal perspectives regarding future clinical applications for therapeutic drug monitoring of A77 1726.

It would be interesting to know whether early decisions on therapy withdrawal or continuation are improved when unblinded, i.e. whether decisions can be based on the combination of insufficient response and a low A77 1726 steady-state serum concentration. Under the assumption of therapy compliance and stable dosing, a direct relationship between duration of therapy, A77 1726 serum concentration at that moment and the A77 1726 steady state serum concentration exists. This leads to the hypothesis that a non-steady state A77 1726 serum concentration determined early in leflunomide therapy, for example after 4 weeks of treatment, may well predict patients response to therapy later on. Applying this hypothesis to leflunomide therapy, theoretically, offers the opportunity to make early decisions based on non-steady state A77 1726 serum concentrations and may prevent delay before therapy is switched to more efficacious alternatives for the individual patient. To what extent this approach will lead to improvements in leflunomide treatment outcomes has to be subject of further studies.

Secondly, one could speculate whether patients with inadequate clinical response to leflunomide treatment and a low, sub-therapeutic A77 1726 serum concentration (< 16 mg/L), 28% of the whole population in our study, will show improved response at increased daily leflunomide doses. Since A77 1726 shows linear pharmacokinetics (a linear relation between dose rate and steady state serum concentrations), an increased dose will lead to higher serum concentrations. With a positive predictive value of 56%, not all patients at A77 1726 serum concentrations ≥ 16 mg/L will become good responders according to DAS_{28}-response criteria. To put the potential role of therapeutic drug monitoring on the basis of our results into perspective: from the fraction of patients with non or moderate response according to DAS_{28}-criteria, approximately 50% will have a A77 1726 serum concentration < 16 mg/L. When increasing the dose for these patients, we expect 56% of them to become DAS_{28} good responders.

A remark has to be placed with this approach. Comparative studies on leflunomide in rheumatoid arthritis so far have used a narrow dose range varying from 5 to 25 mg daily [2]. Despite increased efficacy a daily dose rate of 25 mg is found to be correlated with a higher incidence of ADR [2,9]. Whether toxicity at leflunomide doses > 20-25 mg/day remains a problem when leflunomide doses are increased selectively for those patients with A77 1726 serum concentrations below 16-18 mg/L, has not yet been the subject of clinical studies.

Information on higher dose rates is available from studies in the field of rheumatology [17,18], transplantation medicine [19] and oncology [20]. Recently, results of 11 patients with rheumatoid arthritis treated with 40 mg leflunomide daily for at least 3 months were published [17]. These patients previously tolerated the 20 mg daily dose but still had active disease on this dose. The authors conclude that a daily dose of 40 mg increased effectiveness of the treatment in 6 of 11 patients. Four of 11 patients encountered mild and reversible adverse events after dose escalation. Metzler et al [18] describe a prospective study of leflunomide in 20 patients with Wegener's granulomatosis. Daily doses were increased stepwise to a maximum of 40 mg. These authors conclude that the safety profile of leflunomide was comparable with that found in clinical trials despite the, compared with RA treatment, higher dose levels. Williams et al. [19] describe a retrospective review of 53 liver or kidney transplant recipients receiving leflunomide at maintenance doses of 40-60 mg daily, after receiving loading doses of 1200-1400 mg over 7 days to achieve steady state A77 1726 serum concentrations of 100 mg/L. In their review leflunomide was well tolerated and dose-limiting side effects occurred in less than 15% of patients when drug serum levels were less than 80 mg/L. At these dose rates the authors conclude that patients can be safely dosed during more than 300 days follow-up. Although not directly applicable to a population with RA these data are informative of the safety of dose rates over 20 mg/day.

Conclusion

We have shown that in a steady state there is no association between disease activity and A77 1726 serum concentration. However, lower subtherapeutic A77 1726 serum concentrations are related to absence of response on leflunomide therapy. These results support the conclusion that determination of A77 1726 serum concentrations may influence prescribing procedures and may offer an opportunity for leflunomide treatment optimization.

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Chapter 4

Switching from aurothioglucose to aurothiomalate

Chapter 4.1

Parenteral gold preparations. Effectiveness and safety of therapy after switching from aurothioglucose to aurothiomalate.

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Abstract

Objectives

For reasons of insufficient quality of the raw material, aurothioglucose was withdrawn from the Dutch market at the end of 2001. Aurothiomalate became available as an alternative preparation. We followed a cohort of patients during the first year after switching from aurothioglucose to aurothiomalate to study effectiveness and safety.

Methods

Patients were observed at baseline, and at 3 and 12 months after switching. At each visit, data on adverse drug reactions (ADR) , withdrawal and disease activity were collected.

Results

120 patients (age 63[15] years, 68% female, 93% rheumatoid arthritis, duration of disease 15[9] years, 82% IgM rheumatoid factor positive, 9[9] (range 0.1-45) years of previous aurothioglucose therapy) were included. Nineteen patients (16%) reported an ADR on aurothiomalate not previously experienced on aurothioglucose; pruritus, dermatitis/stomatitis and chrysiasis/hyperpigmentation being most frequently reported. Twenty-nine patients (24%) patients withdrew from aurothiomalate within 12 months follow-up for reasons of ineffectiveness (14%), adverse drug reactions (7%) or disease in state of remission (3%). Kaplan-Meier estimates show aurothiomalate survival rates of 78.5% after 12 months. No statistically significant differences between the disease activity parameters during follow-up visits compared with the baseline visit were detected for the patients remaining on aurothiomalate.

Conclusions

Within the first 12 months after switching from aurothioglucose 24 percent of patients withdrew from aurothiomalate. Sixteen percent of patients reported novel adverse drug reactions. For the population remaining on aurothiomalate no clinically relevant changes in disease activity were recorded after switching.

Introduction

Since 1943, in the Netherlands aurothioglucose (ATG; Auromyose®) was the only parenteral gold preparation available. For reasons of insufficient quality of the raw material, ATG was withdrawn from the Dutch market at the end of 2001. This withdrawal from the market resulted in an estimated 1000 to 1500 patients in the Netherlands switching from ATG to another treatment option.

Although intramuscular gold currently is not the first choice option for rheumatologists in treating patients with rheumatoid arthritis (RA), these preparations remain a part of the treatment paradigm [1]. Studies show effectiveness of intramuscular gold to be similar with methotrexate in different settings [2-4]. Rheumatologists requested for ongoing availability of a parenteral gold salt for prescription purposes. The Dutch Medicines Evaluation Board, after an accelerated procedure, licensed aurothiomalate (ATM; Tauredon®) as an alternative gold preparation as requested.

Both ATG and ATM are studied in over 50 randomized, controlled trials each. Comparable effectiveness of ATG and ATM was shown in a 2-year follow-up study in 125 patients [5]. Results from research studying the switch from ATM to ATG show the latter to be tolerated well after switch [6] or prevent post-injection reactions related to ATM-injections [7]. Although never formally studied, some publications suggest that switching from ATG to ATM may introduce clinical problems. Differences in toxicity have been observed in a study comparing ATM and ATG [5].

To study earlier suggestions of negative safety of the aqueous ATM preparation, we monitored patients switching from the oily ATG preparation Auromyose® to the aqueous ATM preparation Tauredon® in a national case series study in the Netherlands.

Methods

Inclusion

At the moment of withdrawal of ATG (August 2001) rheumatologists in The Netherlands were asked to participate in the study. Patients switching from ATG to ATM were eligible for inclusion. Data analysis was carried out for patients with a complete 12-month follow-up, withdrawal from ATM or death.

Follow-up

Baseline data consisted of patient-, disease- and treatment characteristics. Follow-up visits took place at 3 and 12 months. ADR on therapy were recorded on a standard form, listing 34 different ADR known to be related to gold therapy. Novel ADR were defined as ADR not previously reported at the baseline visit with respect to the ATG treatment. In case of withdrawal from ATM, the time until withdrawal and the reason for withdrawal were recorded. Effectiveness of therapy was recorded as changes in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), a visual analogue score (VAS) of patients and rheumatologists estimation of disease activity, and a categorical (better, equal, worse) estimation of change in disease activity compared with the previous visit by patient and rheumatologist.

ATM-dosing

The ATG-dose was converted to the ATM-dose on a 1:1 milligram basis, since ATG and ATM contain a comparable fraction of elementary gold, 50.3% and 50.5%, respectively. Rheumatologists were allowed to adjust the ATM-dose as needed, adapting frequency of administration or dose per administration.

Statistical analysis

SPSS 12.0.1 for Windows was used for data collection, data validation, data selection, and statistical analysis. Student's t-test was used for comparing mean values of disease activity parameters between visits. Kaplan-Meier estimates were used to calculate the cumulative probability of withdrawal from ATM. The relation between baseline variables and withdrawal from ATM was studied by logistic regression analysis. A p-value < 0.05 is considered significant.

Results

Population

Since most hospitals did not run out of stock of ATG immediately, it lasted up to October 2002 for the last patients to be included. One-hundred-twenty patients were included by 30 rheumatologists in 18 hospitals. Mean [SD] age of the patients was 63[15] years, 68% were female and patients used ATG for 9[9] (range 0.1 - 45) years prior to switching to ATM. The

Table 1. Treatment characteristics at baseline.[1]

Treatment characteristics	
Parenteral gold prescribed as first DMARD (%)	21
Number of DMARDs prior to parenteral gold	1.8[1.5]
Range	0-7
Concomitant corticosteroid use (%)	12
Concomitant other DMARD use (%)	18
Methotrexate	9
Sulfasalazine	3
Hydroxychloroquine	3
Other	3
Indications for gold therapy (%)	
RA	93
JIA	3
AP	3
Other	1
Parenteral gold characteristics	
Duration of ATG treatment (months)	109[109]
Median	75
Range	1-542
Weekly dose of ATG (mg; %)	
< 10	27
≥ 10-<25	30
≥ 25	53
Cumulative ATG dose (mg)	9045[11929]
Median	5300
Range	100-75000

Legend: AP= arthritis psoriatica, ATG=aurothioglucose, DMARD=disease-modifying antirheumatic drug, JIA =juvenile idiopathic arthritis, RA=rheumatoid arthritis. [1]Mean [standard deviation] unless stated otherwise.

Table 2. Novel adverse drug reactions reported in relation to ATM therapy during 12 month follow-up.

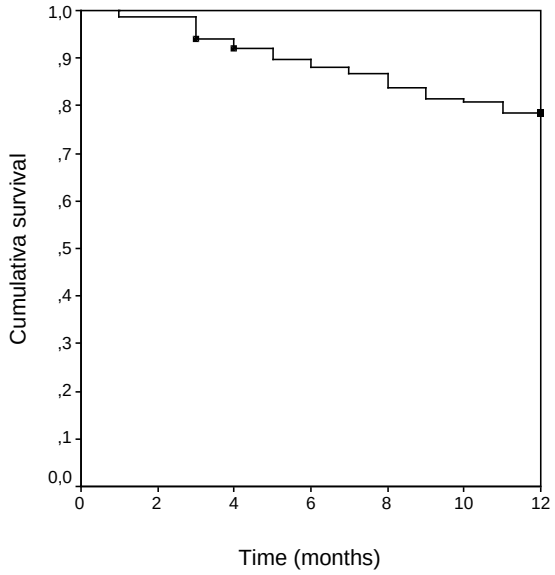
Adverse drug reation	N (%)
Pruritus	8 (7)
Dermatitis/stomatitis	6 (5)
Chrysiasis/pigmentation	5 (4)
Proteinuria	4 (3)
Urticaria	2(2)
Headache	2 (2)
Vasomotor reactions	2 (2)
Arthralgia/myalgia	2 (2)
Palpitations	1 (1)
Mild enterocolitis/upper abdominal complaints	1 (1)
Pain in upper arms	1 (1)

indication for gold therapy was rheumatoid arthritis in 93% of patients, with a mean duration of disease of 15[9] years. Eighty two percent of the patients with rheumatoid arthritis were positive for IgM rheumatoid factor. Table 1 shows the treatment characteristics of the population. Two patients died, respectively 3 and 4 months after switching to ATM, for reasons not related to gold treatment (brain tumor, cardiac arrest). No patients were lost to follow-up.

Adverse drug reactions

Nineteen patients (16%) reported one or more novel ADR during follow-up (Table 2). The patient group reporting a novel ADR during ATM did not statistically significant differ from the patient group not reporting a new ADR with respect to age, gender, IgM rheumatoid factor status, erosive disease, presence of rheumatoid noduli, duration of RA, weekly ATM dose, cumulative ATG dose or number of previous DMARDs. However, patients reporting a new ADR had a longer median duration of previous ATG therapy compared with patients not-reporting a new ADR, 117 and 66 months respectively (p=0.048).

Figure 1. Kaplan Meier estimate of ATM withdrawal.



Legend: ▪ = censored observation

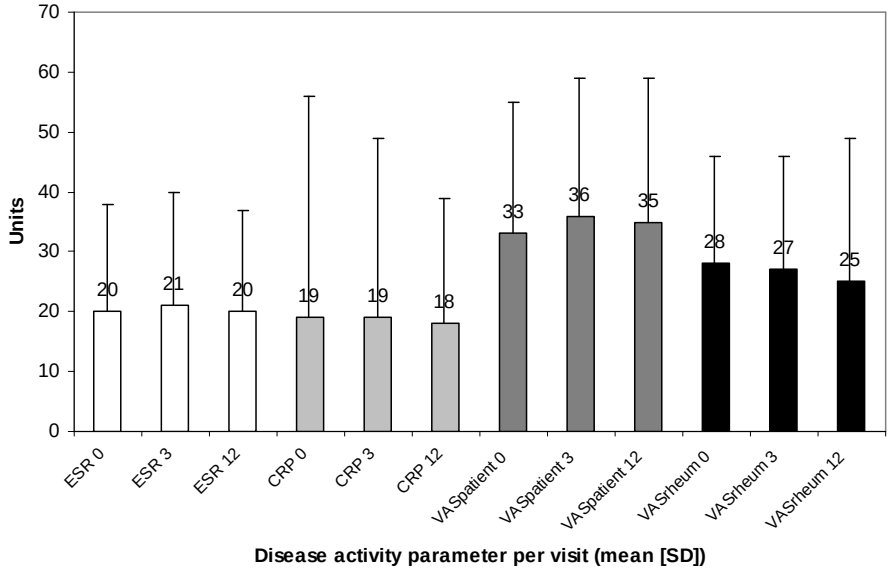
Withdrawal

Twenty-nine (24%) patients withdrew from ATM, after a mean [SD] of 5.9[3.0] months. Reasons for ATM withdrawal were ineffectiveness (14%), ADR (7%), a combination of ineffectiveness and ADR (1%), and RA in remission (3%). Kaplan-Meier estimates for the probability of ATM survival are shown in Figure 1.

Determinants for ATM withdrawal

Of the variables studied age, gender, body mass index, duration of rheumatic disease, presence of rheumatoid nodules, erosive disease, IgM rheumatoid factor status and cumulative ATG dose were found not to be associated with withdrawal. However, duration of ATG therapy > 72 months (relative risk (RR) 3.0 95% confidence interval (CI95) 1.3-6.7) or pretreatment with 1 or 2 disease-modifying antirheumatic drugs (RR 3.3, CI95 1.4-7.6) were found to be predictive for lower withdrawal rates compared with patients on ATG therapy for ≤ 72 months and pre-treatment with >2 disease-modifying antirheumatic drugs, respectively.

Figure 2. Disease activity parameters (values are shown as mean ± standard deviation).



Legend: CRP = C-reactive protein (mg/L), ESR = erythrocyte sedimentation rate (mm/hr), $VAS_{patient}$ respectively VAS_{rheum} = visual analogue scale as recorded by patient respectively rheumatologist (mm, in a 100-mm scale). Numbers accompanying x-axis labels indicate follow duration in months.

Disease activity

Completeness of data on disease activity at each visit was above 80% at every visit for ESR (range 83-100%), VAS as rated by patient (range 80-89%) and VAS as rated by the rheumatologist (range 81-94%). CRP data were recorded in 60-73% of the baseline and follow-up visits. Parameters of disease activity (Figure 2) did not significantly differ between baseline and the follow-up visit after 3 and 12 months, respectively. Patients and rheumatologists ratings of disease activity compared with the baseline visit are shown in Table 3. Patients' ratings tend to worsen during follow-up, rheumatologists' ratings have no tendency for better nor for worse.

Table 3. Patients' and rheumatologists' rating of disease activity compared with baseline visit (%).

	Visit after 3 months	*Visit after 12 months*
Patients rating		
Better	17	7
Equal	46	62
Worse	37[1]	32[1]
Rheumatologists rating		
Better	13	12
Equal	71	73
Worse	16[1]	15[1]

Legend: [1] Percentages including patients withdrawn from treatment for ineffectiveness of therapy.

Discussion

Our study showed that 24% of patients switching from ATG to ATM during a 12-month period withdrew from ATM, mainly for reasons of ineffectiveness or adverse drug reactions. After switching 16% of patients reported novel adverse drug reactions. For the population remaining on ATM no clinically relevant changes in disease activity were recorded.

A head-to-head comparison of ATG and ATM on effectiveness by Rothermich et al. [8] found no significant differences between both gold salts. Our data are in accordance with their study.

Novel ADR most frequently reported on ATM therapy in our study were pruritis and dermatitis/stomatitis. This finding is in accordance with the results from previous studies, with skin eruptions and stomatitis having a 2.8 respectively 3.2-fold higher incidence in the ATM group compared with the ATG group [5,8]. It is important to realize that these results are derived from studies conducted in the 1970's when requirements for study design, follow-up and publication were different compared with today.

Can we explain the higher incidence of stomatitis/dermatitis and pruritis for ATM in comparison with ATG? Firstly, when the gold is involved in these sequelae, then the difference in the pharmacokinetic profiles of the two preparations may play a role. The absorption of ATM from aqueous solutions is known to be very rapid, with gold peak serum

concentrations between 10 minutes and 2 hours [8,9]. Applying the oily vehicle of ATG results in delayed gold peak serum concentrations, and these peak levels may not be reached for as long as 6 to 8 hours after injection. Although several authors conclude that serum gold levels and clinical effectiveness or ADR are not associated [10,11], the high unbound concentration directly after injection of the aqueous solution may explain for the negative safety profile of the aqueous preparations.

Secondly, when thiomalate plays a role in these phenomena, the results of the study by Rudge et al. [12] may be important. They found no correlation between plasma levels or urinary excretion of free thiomalate between patients with and without ADR during ATM therapy, suggesting that thiomalate is not a relevant factor in the occurrence of ADR. Thirdly, Ernestam et al [13] showed *in vitro* production of IL-10 in peripheral blood mononuclear cells to be related with a lack of skin reactions *in vivo*. Whether ATM and ATG have differential effects on IL-10 production and whether they may be an explanation for the differences in the incidence of skin reactions remains to be studied.

How can we interpret the survival rate of ATM after switching from ATG? ATG was withdrawn from the market suddenly and without prior warning to rheumatologists and pharmacists, leaving no opportunity to conduct a comparative, blinded trial for switching from ATG to ATM. Therefore, a comparison of the withdrawal rate, in our study 24% in 12 months, with data from populations in other studies is necessary. When comparing data from other trials with our data two options remain. Firstly, when ATM after switching is considered as *de novo* gold therapy withdrawal data from follow-up of *de novo* gold populations are relevant. Results from these studies show that withdrawal from gold therapy within 12 months vary between 30% and 47% [2,14,15] in patients with rheumatoid arthritis. Secondly, ATM-therapy, after switching from ATG, can be considered a continuation of already installed gold therapy. Specific information on withdrawal rates from gold therapy after long-term follow-up, the mean duration of ATG therapy in our study was 75 months, is not available. However, some data can be derived from long-term follow-up studies in rheumatoid arthritis. Pincus et al [16] reported a withdrawal rate of 24% between 24 months and 60 months of therapy. Estimating an annual withdrawal rate of 8%, assuming an equal percentage of the population withdrawing each year. Galindo-Rodriguez et al [17] reported a withdrawal rate of 13% between 3 and 6 years of gold therapy, estimating an annual withdrawal rate of 4-5%.

Therefore, on the basis of withdrawal rates, ATM therapy after switching from ATG in our study cannot be considered a *de novo* start of gold therapy since the incidence of withdrawal

is lower compared with control populations, nor can it be considered a continuation of gold therapy since the incidence of withdrawal is higher compared with long-term follow-up populations.

At the moment of withdrawal of ATG from the market rheumatologists and their patients had to reconsider treatment options. Possible options were switching from ATG to ATM, withholding treatment or introduction of a non-gold-containing DMARD. Considering the efficacy of newly available options as leflunomide and tumor necrosis factor alpha blocking therapies, it is remarkable that only 24% of patients withdraw from ATM therapy in our study despite the occurrence of novel ADR in some patients. A certain degree of satisfaction with current gold therapy may have played an important role in deciding to continue parenteral gold therapy.

Conclusion

Twenty four percent of patients withdrew from aurothiomalate, mainly for reasons of ineffectiveness (14%) or adverse drug reactions (7%). Within the first 12 months after switching from aurothioglucose to aurothiomalate 16% of patients reported novel adverse drug reactions. For the population remaining on aurothiomalate no clinically relevant changes in disease activity were recorded after switching.

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Chapter 5

Clinical relevance of drug-drug interactions

Focus on rheumatoid arthritis

Chapter 5.1

Clinical relevance of drug-drug interactions: a structured assessment procedure.

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Submitted.

Abstract

Introduction

Computerized drug interaction surveillance systems (CIS) may be helpful in detecting clinical significant drug interactions. Experience with CIS learns that they often yield alerts with questionable clinical significance, fail to provide relevant information on risk factors for the adverse reaction of the interaction and fail to detect all significant drug interactions. These problems stress the importance of transparency and selectivity in choosing the drug interactions to be included in CIS. In the Netherlands the Working Group on Pharmacotherapy and Drug Information is responsible for maintenance of the CIS of the Royal Dutch Association for the Advancement of Pharmacy (KNMP).

Methods

The Working Group developed an evidence-based procedure for structured assessment of drug-drug interactions and revised all drug interactions in the CIS accordingly.

Results

For every drug interaction four core parameters are assessed: evidence on the interaction, clinical relevance of the potential adverse reaction resulting from the interaction, risk factors identifying patient-, medication- or disease characteristics for which the interaction is of special importance and the incidence of the adverse reaction. On the basis of this assessment the drug-drug interactions for introduction in the CIS are selected. After revision of the drug combinations in the CIS of the KNMP the Working Group judged 24% of the combinations not to interact and another 12% to interact but not to require action.

On the basis of this assessment the subset of drug combinations for which interaction alerts are generated and the information on management of a drug interaction alert for users of the CIS were adapted. When an alert is generated by the CIS, the user of the system is supplied with comprehensive information on the four core parameters, the mechanism of the interaction and critical information for management of the interaction for the individual patient.

Discussion

This structured procedure offers the possibility for transparent and reproducible assessment of the clinical relevance of drug interactions.

Conclusion

A CIS selectively generating interaction alerts based on this assessment may help in realizing good clinical practice and offers a methodology to further increase drug safety.

Introduction

Quality of pharmacotherapy is highly dependent on the process of choosing a drug in relation with the nature of the disease. In the process of choosing the optimal pharmacotherapeutical strategy, factors like route of administration, dosage, contra-indications, the potential for adverse drug reactions and costs play an important role. The possibility of drugs to influence each others safety or effectiveness, a drug-drug interaction, is an additional variable in making the optimal choice for pharmacotherapy.

Drug interactions increase morbidity and mortality and may lead to hospital admission [1-4]. In primary health care 9-70% of patients are reported to be exposed to drugs with the risk of a drug interaction, with 1-23% of major relevance [5-10]. A French study reports an incidence of 27 per 10,000 prescriptions with contra-indicated drug interactions in an ambulatory outpatient population [11]. During hospital admission the number of drug interactions per patient increases, with potential clinically relevant drug interactions occurring in 1 out of 70 prescriptions [12,13].

Many sources for information of drug interactions are available for health care providers, ranging from the summaries of product characteristics and product leaflets to text books and internet sites (gsm.com, epocrates.com, fda.gov, arizonacert.org) [14-16]. However, knowledge of an interaction between two drugs is no guarantee for timely recognition of the interaction or for taking the appropriate action to prevent the risk of an adverse outcome [17,18]. Unless the major advances in our understanding of drug-drug interactions, our ability to appropriately apply this information to specific patients has lagged far behind [19,20].

Computerized drug interaction surveillance systems (CIS) may be helpful in detecting and preventing drug interactions with clinical significance [21]. However, many pharmacists and doctors experience these systems to yield a large number of drug interactions with questionable or unclear clinical significance, fail to provide identifiable patient and medication risk factors, fail to detect all relevant drug interactions and to include a variable set of interactions [18,22-25]. These shortcomings lead users to be uncertain on the quality of the system and to ignore drug interaction alerts [23,25]. Furthermore, one study shows that interpretation of drug interaction signals without clear information on background and clinical relevance leads to discrepancies in perception of seriousness of the interactions [26].

These problems stress the importance of transparancy and selectivity in choosing the drug interactions to be included in CIS. The Working Group on Pharmacotherapy and Drug

Information is responsible for maintenance of the CIS of the Royal Dutch Association for the Advancement of Pharmacy (KNMP). In this 22-member multidisciplinary Working Group internists, general practitioners, pharmacists, hospital pharmacists, clinical pharmacologists and (a member of) the Netherlands Medicines Evaluation Board are represented. The Working Group recently developed a procedure for structured assessment of drug-drug interactions. On the basis of this assessment, drug interactions for inclusion in the KNMP-CIS, with widespread use by general practitioners and (hospital) pharmacists, are selected.

In the Netherlands tracking of virtually complete prescription data is possible since patients usually register with one pharmacy only and local pharmacies keep a computerised, detailed record of all delivered prescriptions. For this reason electronic medication surveillance for the complete drug use profile of the individual patient is possible.

In this manuscript we describe the procedures for structured assessment of drug-drug interactions and the translation of this assessment to the CIS of the Working Group on Pharmacotherapy and Drug Information in the Netherlands. Further, we present the results of the revision of the complete CIS of the Royal Dutch Association for the Advancement of Pharmacy on the basis of these assessments.

Structural assessment

Goals

To develop a system for structured assessment of drug interactions it is important to define the goal of drug interaction alerts. The Working Group defined this goal as ‘timely recognition of the opportunity to intervene in drug use in order to prevent an undesired effect as a result of a combination of drugs’. This definition clearly states that a drug interaction alert is useful only when an intervention is necessary and possible, for example prescribing and/or dispensing an alternative drug, dosage adjustment or adjusted monitoring of drug effects. The Working Group stated that users of the CIS should be presented drug interaction alerts requiring a potential intervention, accompanied with appropriate information on the relevance for their individual patient and with a clear proposal for potential interventions. Furthermore, the assessment procedure should facilitate quick updates of the CIS when new drug interactions are recognized or new information on existing drug interactions is published.

Table 1. Core parameters for assessing the clinical relevance of drug interactions.

Core parameters
Evidence on the drug interaction
The clinical relevance of the potential adverse reaction resulting from the drug interaction
Risk factors, the drug interaction may be of special importance in patients with the specific risk factor
Incidence of the adverse reaction given the combination of the drugs

Core dataset

For the assessment of drug interactions the Working Group defined four core parameters (Table 1). When assessing these four parameters for every potential drug interaction, a complete and transparent set of information is collected which can be used as the basis for management of the drug interaction. Information on these parameters is collected and prepared by pharmacists from the Scientific Institute for Pharmacists in the Netherlands and presented to the Working Group every 6 weeks. In the Working Group, on the basis of these four core parameters, clinical relevance is discussed in a multidisciplinary way.

Evidence

The first suggestions that a drug interaction exists often comes from the registration file and summary of product characteristics of newly registered drugs. The importance of structured research on drug interactions in the pre-registration phase is stressed by the Note for Guidance on the 'Investigation of drug interactions', giving guidelines for studies on drug interactions [27]. Despite this research, problems arise in gaining insight in the background information to assess the clinical relevance of these drug interactions. Evidence on the drug interaction may be theoretical, or the evidence is derived from clinical research that is not published and not freely accessible (data on file). In assessing the clinical relevance of newly registered drugs the standard operating procedure of the Working Group is to ask the registration holder of the drug for detailed information on the drug interaction, besides searching a standard set of sources (Table 2).

Once papers have been selected as potential sources of evidence on the drug interaction, the Working Group uses an 5-category scale for assessing the quality of the evidence for a drug interaction derived from [32] (Table 3).

Table 2. Sources for drug interactions referred to by the Working Group on Pharmacotherapy and Drug Information.

Information sources
Drug interaction text books [14,15]
Pubmed database [28]
Excerpta Medica database (EMBASE) [29]
Iowa Drug Information System (IDIS) [30]
European Public Assessment Reports (EPARs) [31]

Some drug interactions lack evidence from studies or case reports but have theoretical considerations as the primary basis, for example in cases where an analogy is suspected with another representative of the same drug class which is known to have a drug interaction. For interactions suspected to be relevant on the basis of an analogy the Working Group requires detailed information on the mechanisms of the interaction to consider the drug interaction to be relevant. For example, the HMG-co-enzyme A-inhibitors (‘ statins’) are known to have differential inhibiting effects on the cytochrome P450 enzyme system. Handling the statins as a homogenous group when considering drug interactions and the cytochrome P450 system therefore, is incorrect.

The potential adverse reaction

The second core parameter considered by the Working Group is the clinical relevance of the potential adverse reaction from the drug interaction.

The Note for Guidance on the investigation of drug interactions defines a drug interaction as clinically relevant ‘when the therapeutic activity and/or toxicity of a drug is changed to such an extent that a dosage adjustment of the medication or medical intervention may be required’ [27]. This relevance often strongly depends on individual patient- or disease-characteristics. A dichotomous categorization of the drug interaction as relevant or irrelevant is an undesired oversimplification of drug interaction assessment. To obtain a useful, transparent and reproducible result the Working Group uses a 6-category scale for the seriousness of the adverse reaction of a drug interaction. The effect of the drug interaction as reported in the evidence on the drug interaction forms the basis of the classification of the effect. The categories, named A to F, are ordered at increasing seriousness (Table 4).

Table 3. Categories for quality of evidence.

Category	*Description*
0	Pharmacodynamic animal studies; in vitro studies with a limited predictive value for the human in vivo situation; data on file
1	Incomplete, published case reports (no re- or dechallenge, presence of other explaining factors for the adverse reaction)
2	Well-documented, published case reports; retrospective analyses of case series
3	Controlled, published interaction studies in patients or healthy volunteers with surrogate end points
4	Controlled, published interaction studies in patients or healthy volunteers with clinically relevant end points
Variable	Posters and abstracts from scientific meetings: 0 or 1, depending on the information provided. When the information of the poster or abstract is not published in a peer reviewed journal within 3 years after the scientific meeting, this information is re-categorized as 0.
Variable	Information from the Summary of Product Characteristics/European Public Assessment Reports (EPAR): 0, 1 or 2, depending on the information provided [31].
Variable	Retrospective case series: 2 or 3, depending on the information provided.

The Working Group discusses for each new adverse reaction, in which category the reaction has to be placed. By categorizing effects of drug interactions and using earlier classifications of adverse reactions for assessment of new drug interactions, a reproducible system of categorization of drug interactions effect has been developed.

Some adverse reactions, like changes in blood pressure, changes in International Normalized Ratios (for oral anticoagulants), can have different gradations in seriousness. For categorization of these effects the Working Group uses the Common Toxicity Criteria as developed by the National Cancer Institute (NCI-CTC) [33]. The NCI-CTC use a 6-step scale for dividing gradual adverse reactions of drugs, 0-5, which are translated to A-F in the system of the Working Group.

Risk factors

The risk of an adverse outcome from drug interactions may depend on patient- (e.g. age, gender), disease- (e.g. renal and hepatic function) and medication- (e.g. dose, route of administration) characteristics. Information on these risk factors is essential information for

Table 4. Examples of effects per category of seriousness of adverse reactions due to drug interactions.[1]

Category A	- Clinically irrelevant effect
	- Failure of therapy with: digoxin
	- Ventricular premature beats, atrial ectopics
	- Increase of international normalized ratio up to 4.0
Category B	- Adverse reactions due to increased bio-availability of calciumantagonists of the dihydropyridine class
	- Misscelaneous : amnesia, fatigue, headache, nausea
Category C	- Adverse reactions due to increased bioavailability of anti-epileptics, ciclosporin, tacrolimus, sirolimus
	- Increased risk of failure of therapy: methadone, leflunomide, iron suppletion, levothyroxin, antidepressants
	- Parkinsonism, tremor
	- Increased risk for upper gastro-intestinal bleeding
Category D	- Adverse reactions due to increased bioavailability of aminoglycosides, ciclosporine, lithium, methotrextate, digoxin
	- Increased risk of failure of therapy for a serious, non-lethal disease; e.g. levodopa, methyldopa, loop diuretics
	- Deep venous thrombosis
	- Convulsions
Category E	- Increased risk of failure of life-saving therapy; e.g. antiretroviral medication, quinidine, rejection-prevention (ciclosporin, tacrolimus, sirolimus)
	- Misscelaneous: prolonged QT-interval, pulmonary embolism, rhabdomyolysis, multi-organ failure
Category F	- Death
	- Torsades de pointes, ventricular tachycardia
	- Misscelaneous: increased risk for pregnancy with risk factors for the fetus/neonate, bone marrow depression, serotonine syndrome

[1] Per category examples of potential effects within the category are shown. In every effect category new events are added after assessment by the Working Group

the user of the CIS. The Working Group, while assessing the relevance of a drug interaction, gathers information on factors predictive for an adverse outcome.

Incidence

Not for every patient an interacting combination of drugs will lead to an adverse outcome. The Working Group, while assessing the relevance of a drug interaction, gathers information on the incidence of adverse outcomes. In many cases information on the incidence of the adverse outcome is lacking, due to the absence of interaction studies.

Results of assessment

Based on the information on the four core parameters the Working Group assesses whether the combination of drugs gives an interaction (interaction: yes or no) and whether this combination of drugs has to be alerted at the moment of recognition by the CIS (action: yes or no).

Interaction yes-action yes

A drug combination that the Working Group assesses to be interacting (interaction: yes) and for which direct alerts have to be generated (action: yes), is entered in the CIS.

It is rare for the evidence to show clearly and unambiguously what the final assessment of the drug interaction should be. Consequently, it is not always clear to those who were not involved in the discussion, how the working Group was able to arrive at its recommendation. In order to address this problem, in accordance with the procedures adopted by the Scottish Intercollegiate Guidelines Network (SIGN; www.sign.ac.uk) the Working Group has introduced the concept of considered judgement. Under considered judgement, the Working Group summarises its view of the total body of evidence on the drug interaction. This summary covers the four core parameters of the assessment process. Besides this summary, when alerting a drug interaction, the surveillance system generates a text for the user to aid in the process of managing the interaction. Four different texts are provided by the Working Group: a prescriber text, a pharmacy counter text, a hospital text and a background information text.

The prescriber text gives an alert and information for the prescribing physician. This text takes into account the possibility to prescribe an alternative medication or to adjust therapy monitoring. The pharmacy counter text gives information relevant at the moment of dispensing of the drug in the pharmacy. From our experience in the past years a third text dedicated to the clinical situation, the hospital text, is provided.

Besides the prescriber-, pharmacy counter- and hospital text, all users of the CIS can consult a fourth text, the general background information text. This text offers information on the four core parameters as assessed by the Working Group, besides information on the mechanism of the interaction and a short review of the literature on the interaction. Quality of evidence on the drug interaction and the seriousness of the adverse outcome are transparently translated to the user as an alphanumeric code, 0A (evidence lacking, clinically irrelevant effect) to 4F (evidence consists of controlled, published interaction studies with a clinically relevant end point; the adverse outcome is clinically very relevant). Together with the risk factors and the incidence of an adverse outcome the user of the surveillance system is presented core information on the drug interaction in a transparent and concise manner in case of an alert.

Interaction yes-action no

When the Working Group assesses a combination of drugs to be interacting (interaction: yes) but requires no action (action: no) when the combination of drugs is prescribed this combination of drugs is entered in the surveillance system. However, for these interactions the CIS will not automatically generate an alert. Instead, these interactions are only logged by the system. The reason to enter these drug combinations in the interaction surveillance system is the possibility for users of the CIS to create a tailor-made system, that is they have the possibility to generate an alert for these combinations in their local situation.

Interaction no

When the Working Group assesses the combination of drugs not to be interacting (interaction: no) and no action is therefore required, the drug combination will not automatically generate an alert. In these cases users of the CIS do not have the possibility to generate an alert for the combination.

Table 5. Examples of drug interactions per category.

A. Interaction yes, action no

Bile salts binding resins + cholesterol-lowering fibrates

Cimetidine + erythromycine

Cimetidine + calcium antagonists of the dihydropyridin class

Ciclosporin A + quinolone antibiotics

Risperidone + selective serotonine reuptake inhibiting antidepressants

B. Interaction no

Bisacodyl (oral route) + antacids

Linezolide + sertraline

Lithium + trimethroprim

Monoamine oxidase inhibitors + non-SSRI antidepressants

Moclobemide + tramadol

Pimozide + antimycotics of the azole-class

Terfenadine + fluoxetine/fluvoxamine

Tetracyclines + sucralfate

In a separate drug information system published by the Royal Dutch Association for the Advancement of Pharmacy, the Informatorium Medicamentorum, information on these drug combinations is gathered [34]. Publication in this medium provides the opportunity for users to detect whether a drug combination has been assessed by the Working Group and provides complete information on all four core parameters.

Revision of the drug interactions the KNMP-CIS

On the basis of this structured assessment the Working Group in 2002-2003 revised the complete set of drug combinations present in the CIS of the KNMP. Exceptions were made for the interactions concerning oral anticoagulants and antiretroviral medication since these interactions were assessed in close cooperation with the Federation of Thrombosis Services

in the Netherlands and experts in the field of treatment of HIV-infections, respectively. Revision of these combinations is currently ongoing.

Before revising the CIS of the KNMP the system included 225 different drug combinations. After revision according to the structural assessment the Working Group judged 54 (24%) of these combinations not to be interactions. This subset of combinations was withdrawn from the CIS. Of the remaining 171 combinations, 26 (12%) were judged to be interactions but requiring no action. These combinations were left in the CIS but no alert is generated when the combination is recognized. For the remaining 145 combinations (64%) an alert is generated as soon as the combination is detected by the CIS. For combinations judged to be not interacting or interacting but without the necessity for direct action, examples are given in Table 5.

Discussion

We described the procedure for structured assessment of drug interactions by the Working Group on Pharmacotherapy and Drug Information of the Royal Dutch Association for the Advancement of Pharmacy and the procedures to inform the users of the CIS on the interpretation of the results of the assessment for their individual patients.

The Working Group adopted the procedure for structured assessment of drug interactions in 2002 and revised the complete CIS accordingly. This resulted in 36% of the combinations being assessed as ‘not interacting’ or ‘interacting but not requiring any action’. This percentage is comparable with the results of a German group that concluded that the number of alerts would be reduced by approximately 30% when drug pairs were filtered out that do not require active management as a result of minor or unspecified severity [19].

Since the revision all new drug interactions have been entered into the CIS only after completing the structured assessment procedure. Experience with the procedure since 2002 shows that major goals for the assessment procedure are reached. Adverse reactions are reproducibly categorized, re-assessment of drug interactions on the basis of new information is a rapid process and the structured assessment facilitates the translation of the information from the four core parameters to clinical action.

As the authors from a recently published study concluded, over 75% of major drug interactions with published evidence are manageable, that is adverse reactions can be prevented by taking specific actions [19]. Manageability is highly dependent on facilitation of

the process of adequately informing the users of the CIS and critically selecting the combinations for which alerts are of clinical significance. A CIS generating specifically clinically significant alerts, accompanied with adequate information, may offer a tool for further optimization of quality of pharmacotherapy.

It is important to recognize that the quality of evidence supporting drug-drug interactions may differ between drugs registered before the publication of the 'Note for guidance on the investigation of drug interactions' and drugs registered after this Note for Guidance gave guidelines for research on interactions [27]. However, public availability of the information from drug-interaction studies is important, instead of these results remaining 'data on file' or short descriptions in the summaries of product characteristics and EPARs.

It has to be taken into account that CIS are no substitute for the information in the product leaflets. However, since information in the product leaflet often is too comprehensive to assess the relevance of a drug interaction for the individual patient, an alert from the CIS provides additional information to the text of the product leaflet.

Theoretically, information on pharmacogenetic testing, for example on enzyme and receptor mutations, may introduce benefits in recognizing patients at increased risk of adverse reactions due to drug-drug interactions. However, at the moment pharmacogenetic testing is not part of routine clinical practice and therefore not applicable. When this information becomes important in daily practice, inclusion in the assessment procedure as described above can be easily realized.

Conclusion

The procedure for assessment of clinical relevance of drug interactions as described in this manuscript offers the possibility for transparent and reproducible assessment of the clinical relevance of potential interacting drug combinations. A CIS selectively generating interaction alerts based on this assessment may help in realizing good clinical practice and offers a methodology to further increase drug safety.

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Chapter 5.2

A multidisciplinary approach for the assessment of drug interactions with disease-modifying antirheumatic drugs.

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Submitted.

Abstract

Objectives

Drug-drug interactions (DDI) may adversely influence treatment outcomes in patients with rheumatic diseases. To prevent adverse drug reactions or therapeutic failure timely recognition and adequate management of clinically relevant DDI is required. The objective of this study is to give an overview of drug-interactions with disease-modifying antirheumatic drugs (DMARDs), to assess the clinical relevance of potential drug-interactions with DMARDs and to study the uniformity in assessment of clinical relevance between rheumatologists and hospital pharmacists.

Methods

Potential DDI were selected from product leaflets and search of the medical literature. For every potential interaction, data on the evidence of the DDI, the severity of the adverse reaction from the DDI, risk factors for and incidence of adverse reactions as a consequence of the DDI were collected. Based on this information two observer groups, rheumatologists and hospital pharmacists, independently assessed whether the individual combinations interacted. As a marker for clinical relevance the panel judged whether the combination required immediate intervention.

Results

A total of 40 drug combinations with a DMARD were selected, of these 17 (43%) were judged to be interacting and to require immediate intervention, 13 (32%) were judged not to be interacting or to be interacting but not to require immediate intervention and for 10 combinations (25%) hospital pharmacists and rheumatologists did not agree. Observer agreement between groups for the assessment of the drug combinations to be interacting or requiring immediate intervention showed good (κ= 0.80) and fair (κ= 0.39) agreement, respectively. Rheumatologists tended to require immediate intervention more often for DDI based on increased toxicity of the DMARD as the major adverse reaction, while hospital pharmacists tended to judge DDI with an increased risk of DMARD failure more often to require immediate intervention.

Discussion

Alerts generated by computerized drug interaction alert systems (CIS) have to be specific (generated only when relevant), sensitive (generated in all relevant situations) and have to be accompanied by information for adequate management for the individual patient. In our study for 25 percent of the drug combinations with DMARDs the observer groups did not

agree as to whether the combination required immediate intervention. Due to differences in perception of severity of the effect of a DDI, perceived specificity and sensitivity of alerts generated by CIS may be suboptimal.

Conclusion

For a subset of 10 of 40 DMARD combinations, rheumatologists and hospital pharmacists differed in the assessment of clinical relevance. Multidisciplinary discussion as the basis for uptake of DDI in a CIS may increase sensitivity and specificity of the alerts generated by a CIS.

Introduction

Pharmacotherapy is the mainstay of the treatment of rheumatoid arthritis. Due to higher age and the presence of comorbidity in the population treated, many patients are prone to be treated with multiple drugs and therefore are at risk for the adverse reactions due to drug-drug interactions (DDI) [1,2]. To prevent these adverse reactions prompt recognition and adequate management of clinically relevant DDI is required.

Although information on potential DDI is available from reviews [3-6], product leaflets, textbooks [7,8] and medical literature, a number of problems exist concerning recognition of DDI. Manual recognition of potentially relevant DDI, in contrast to computer-generated alerts, has shown to yield incomplete results, with large variety between individual observers [9]. Although computerized drug interaction alert systems (CIS) may improve sensitivity of the recognition of potential relevant DDI, they have a number of major drawbacks [10-14]. Many pharmacists and doctors experience these systems to yield a large number of DDI with questionable or unclear clinical significance, but on the other hand fail to detect all relevant DDI. Further, these systems are reported to fail to provide identifiable patient and medication risk factors. These shortcomings lead users to be uncertain of the quality of the system and to ignore DDI alerts [12,14].

For these reasons a transparent and reproducible assessment of potential DDI is essential before drug combinations are entered into CIS. The Working Group on Pharmacotherapy and Drug Information, responsible for the maintenance of the CIS of the Royal Dutch Association for the Advancement of Pharmacy, developed a structured assessment for DDI to reach this goal. The assessment is based on evaluation of four core parameters of an interacting drug combination: the quality of the evidence on the DDI, the severity of the adverse reaction of the DDI, patient-, medication- or disease characteristics increasing the risk of adverse reactions to the combination and the incidence of the adverse reactions when the combination is given [15]. On the basis of this assessment drug combinations are selected for incorporation in the CIS.

Although the perception of sensitivity and specificity of the alerts generated by the CIS may improve using a structured assessment procedure, differences in assessment of clinical relevance between medical and pharmacological specialties may exist. When these differences are not considered the specificity and sensitivity of the CIS alerts may be perceived as suboptimal. Studies on differences in the assessment of clinical relevance of DDI in rheumatology between observer groups have not been published, to our knowledge.

We performed a study comparing rheumatologists' and hospital pharmacists' assessments of the clinical relevance of DDI as potentially evoked by combining DMARDs and co-medication.

Methods

Selection of potential drug-drug interactions

From product leaflets and text books on DDI [7,8] potential DDI with drugs used as DMARDs were selected. Medical literature was searched using Medline [16] and EMBase [17], using the following search terms for the key word, title and abstract sections of the publications: 'interaction(s)', 'DMARD', 'disease-modifying antirheumatic drug(s)', 'antirheumatic', 'rheumatology', 'rheumatoid arthritis' or the names of the individual DMARDs of interest (anakinra, IL1-RA, auranofin, aurothioglucose, aurothiomalate, azathioprine, D-penicillamine, etanercept, gold, (hydroxo)chloroquine, infliximab, leflunomide, methotrexate, sulphasalazine/sulfasalazine). Reference lists of the retrieved publications were searched for further information on potential DDI.

From all potential DDI with DMARDs the following were excluded:

1. combinations of 1) two DMARDs, 2) DMARDs and systemic corticosteroids and 3) DMARDs and non-steroidal anti-inflammatory drugs, since in the majority of cases these medications are combined intentionally, in order to obtain a better clinical response. Although we were well aware of the existence of the potentially clinically relevant DDI between methotrexate and non-steroidal anti-inflammatory drugs, especially when two different physicians prescribe these medications for the same patient, this combination is not assessed in this study,
2. potential DDI with ciclosporine A. These combinations generally are well-studied, pharmacokinetic DDI and require therapeutic drug monitoring as intervention to manage potential adverse reactions or therapy failure,
3. combinations where the evidence on a potential DDI is based on dose levels far higher than used in the treatment of rheumatoid arthritis. For example, potential DDI with MTX or azathioprine in doses used in oncology or chloroquine as an antimalarial agent,
4. combinations of DMARDs and food-supplements, phytotherapeutic/homoeopathic preparations,
5. pharmaceutical DDI, i.e. (in)compatibilities in pharmaceutical containers.

Table 1. Quality level of evidence.

Category	*Description*
0	Pharmacodynamic animal studies; in vitro studies with a limited predictive value for the human in vivo situation; data on file
1	Incomplete, published case reports (no re- or dechallenge, presence of other explaining factors for the adverse reaction)
2	Well-documented, published case reports; retrospective analyses of case series
3	Controlled, published interaction studies in patients or healthy volunteers with surrogate end points
4	Controlled, published interaction studies in patients or healthy volunteers with clinically relevant end points
Variable	Posters and abstracts from scientific meetings: 0 or 1, depending on the information provided. When the information of the poster or abstract is not published in a peer reviewed journal within 3 years after the scientific meeting, this information is re-categorized as 0.
Variable	Information from the Summary of Product Characteristics/European Public Assessment Reports (EPAR): 0, 1 or 2, depending on the information provided [31].
Variable	Retrospective case series: 2 or 3, depending on the information provided.

Assessment of potential drug interactions

Standard information set per interaction

For every potential DDI a standard dataset was prepared containing comprehensive information on four core parameters of the DDI:

1. Quality of the evidence on the combination, categorized 0-4 (Table 1).
2. Description of the adverse reaction of the combination and the mechanism of the DDI.
3. When the risk of an adverse reaction from the potential DDI is dependent on patient- (e.g. age, gender), disease- (e.g. renal and hepatic function) and medication- (e.g. dose, route of administration) characteristics, these risk factors are given.
4. The incidence of the adverse reaction when the combination is administered.

Further, the standard dataset contained the main publications on the DDI. These publications could be supportive for or deny the existence of the DDI.

Expert assessment

On the basis of the standard dataset per potential DDI, three rheumatologists and three hospital pharmacists were all asked to assess the DDI independently. The rheumatologists and hospital pharmacists were selected on the basis of > 5 years of clinical experience and current involvement in clinical practice. The rheumatologists and hospital pharmacists all worked in large, non-academic teaching hospitals spread throughout the Netherlands.

Assessment took place according to two questions that had to be answered with yes or no.

1. On the basis of the information on the DDI do you assess this combination of drugs to interact? In other words: does anything happen when the two drugs are combined in comparison with the situation were both drugs are administered alone?
2. When you judge this combination to be an interaction, is any immediate intervention required? Immediate intervention is defined as any action required at the moment the combination is recognized, to assure safe and effective use of the combination. Potential immediate interventions include, adjusted monitoring of therapy effectiveness or safety in the near future, adjusted patient information, appointments for therapeutic drug monitoring, dose adjustments or prescription of an alternative drug.

Data analysis

For both observer groups, rheumatologists and hospital pharmacists, the data from the assessment were pooled separately. Outcomes per group were based on the opinion of the majority. On the basis of these assessments the potential DDI were divided into 3 groups:

1. Combinations judged by both observer groups as DDI that require immediate intervention.
2. Combinations judged by both observer groups a) to be not interacting and therefore not to require immediate intervention and b) combinations judged to be interacting but require no immediate intervention.
3. Combinations where rheumatologists and hospital pharmacists disagreed on whether the combination interacted or whether immediate intervention had to be taken.

The adverse reaction of each individual drug combination was prospectively categorized in one of five categories: increasing toxicity of the DMARD or the non-DMARD, decreased effectiveness of the DMARD or the non-DMARD, or other. When the adverse reaction of the

DDI was increased toxicity, and this toxicity was also associated with the DMARD and the non-DMARD individually, this toxicity was categorized as ‘increasing toxicity of the DMARD’.

Statistical analysis

Assessments of the drug combinations per observer group were presented using 2x2 tables. From these, to assess the interobserver variability, Cohen’s kappa was calculated. Kappa values <0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80 and 0.81-1.00 were classified as poor, fair, moderate, good or very good agreement between the two observer groups, respectively [19]. Differences in assessments of clinical relevance between observer groups per adverse reaction category were analysed using the nonparametric McNemar test. A p-value < 0.05 was considered significant.

Results

Selection of potential DDI

Forty potentially interacting drug combinations with DMARDs were found within the selection criteria. For the newer DMARDs in use during the last five years, none of the combinations concerned the group of ‘biologicals’ (anti-tumor necrosis factor therapy, IL-1-RA-therapy). For leflunomide 4 potential interacting combinations were found.

The highest level of evidence found for the selected drug combinations was 3, 2, 1, and 0 for 57, 5, 18 and 20%, respectively. For none of the drug combinations interaction studies with clinical end points, level 4 evidence, was found.

Assessments

Table 2 shows the 2x2 table for the assessment by the two observer groups whether or not the drug combinations are interactions. The results represent good agreement between observer groups ($\kappa = 0.80 \pm 0.11$). Within the observer groups the 40 combinations were judged unanimously in 29 (73%) and 26 (65%) of the cases by hospital pharmacists and rheumatologists, respectively.

Table 3 shows the 2x2 table for the assessment by the two observer groups whether or not the drug combinations required immediate intervention. The results represent fair agreement between observer groups ($\kappa = 0.39 \pm 0.15$). Within observer groups the 40 combi-

Table 2. 2x2 table for assessment: combination interacts yes or no.

		Rheumatologists		*Total*
		No	*Yes*	
Hospital pharmacists	*No*	8	3	11
	Yes	0	29	29
Total		8	32	40

Table 3. 2x2 table for assessment: requiring immediate intervention yes or no.

		Rheumatologists		*Total*
		No	*Yes*	
Hospital pharmacists	*No*	13	5	18
	Yes	5	17	22
Total		18	22	40

nations were judged unanimously in 27 (69%) and 17 (43%) of the cases by hospital pharmacists and rheumatologists, respectively.

Tables 4-6 show specific information per drug combination judged to require immediate intervention, not to require immediate intervention or combinations where both observer groups disagreed.

Rheumatologists tended to require immediate intervention more often for drug combinations with an increased risk of toxicity of the DMARD compared with hospital pharmacists. Rheumatologists and hospital pharmacists tended to differ in their assessments of individual drug combinations where the adverse reaction is decreased effectiveness of the DMARD, with the hospital pharmacists more often judging the combination to require immediate intervention (Table 7).

Table 4. Drug combinations assessed to be interactions requiring immediate intervention.

DMARD	*Combining agent*	*Level of evidence*	*Adverse reaction*	*Ref.*
Azathioprine	Allopurinol	3	↑ azathioprine toxicity	[20,21]
	Doxorubicin	3	↑ hepatotoxicity	[22]
	Oral anticoagulants	2	↓ anticoagulant activity	[23]
Chloroquine	Praziquantel	3	↓ AUC praziquantel by 65%	[24]
	Drugs that increase the QT-interval	0	↑ cardiac arrhythmia	-
D-penicillamine	Digoxin	3	↓ AUC digoxin by 40-64%	[25]
	Iron-salts	3	↓ AUC D-penicillamine by 35-60%	[26]
Hydroxychloroquine	Cardiac glycosides	2	↑ Cmax digoxin by 4-fold	[27,28]
Leflunomide	Activated charcoal/ resins	3	↓ plasma half life of A77 1726, 10-fold	[29]
	Warfarin	1	↑ anticoagulant activity	[30]
Methotrexate	Acitretin/retinoids	3	↑ hepatotoxicity due to ↑ AUC MTX	[31,32]
	Cotrimoxazole/ trimethoprim	3	↑ bone marrow depression	[33-35]
	Isoniazid	3	↑ hepatotoxicity	[36]
	Probenecid	3	↑ C_{24h} MTX 3-4 fold	[37,38]
Sulfasalazine	Digoxin	3	↓ AUC digoxin by 50%	[39]
	Isoniazid	3	↑ hepatotoxicity	[35]
	Talinolol	3	↓ AUC talinolol by 90%	[40]

Legend: ↑ = increase or increased risk, ↓ = decrease or decreased risk, A77 1726 = active metabolite of leflunomide, AUC = area under the curve as a measure of bioavailability, Cmax = maximal plasma concentration, C24h = concentration at 24 hours after administration, MTX= methotrexate, Ref. = references.

Table 5. Drug combinations assessed NOT to require immediate intervention.

DMARD	*Combining agent*	*Level of evidence*	*Adverse reaction*	*Ref.*
Aurothiomalate	ACE-inhibitors	1	Nitritoid reactions	[41,42]
Azathioprine	Lamivudine	1	↑ pancreatitis	[43]
	Mycofenolate mofetil	0	↑ haematological toxicity	[44]
	ACE-inhibitors	3	↑ neutropenia and ↑ anaemia	[45,46]
Chloroquine	Codeine	None	↓ analgesic effectiveness of codein	[44]
	Metronidazole	1	Acute dystonia	[47]
	Neuromuscular blocking agents	0	↑ neuromuscular blockade	[48]
	Mefloquine	0	↑ QT-interval prolongation, ↑ convulsion, ↑ mefloquin plasma concentrations	[49]
D-penicillamine	Clozapine	0	↑ agranulocytosis	[50]
	Oral contraceptives	1	↑ macromastia	[51]
	Tricyclic antidepressants	0	↑ myasthenia gravis	[52]
Gold salts	Chelating agents	0	Changes in gold distribution and elimination	[44]
Methotrexate	Theophyllin	3	↓ theophylline clearance	[53]

Legend: ↑ = increase or increased risk, ↓ = decrease or decreased risk, ACE = angiotensin-converting enzyme, Ref. = references.

Table 6. Combinations were rheumatologists and hospital pharmacists disagreed on whether immediate intervention had to be taken.

DMARD	*Combining agent*	*Evidence*	*Adverse reaction*	*Immediate intervention ?*		*Ref.*
				Hospital pharmacists	*Rheumato-logists*	
Azathioprine	Co-trimoxazole	3	↑ neutropenia/ thrombocytopenia	Yes	No	[54]
Chloroquine	Cimetidine	3	↓ elimination chloroquine	No	Yes	[55]
	Mg-trisilicate/ kaolin	3	↓ AUC chloroquine	Yes	No	[56]
D-penicillamine	Antacids	3	↓ AUC D-penicillamine by 30-40%	Yes	No	[57]
	L-dopa	1	↑ AUC L-dopa by 50%	No	Yes	[58]
Leflunomide	Itraconazole	1	↑ hepatotoxicity	No	Yes	[59]
	Rifampicin	3	↑ Cmax A77 1726 by 40%	No	Yes	[60]
Methotrexate	Penicillins	3	↑ MTX toxicity	No	Yes	[61,62]
Sulfasalazine	Ampicillin/ rifampicin	3	↓ AUC sulfapyridine by 60-65%	Yes	No	[63,64]
	Iron-salts	3	↓ C5h sulfasalazine	Yes	No	[65]

Legend: ↑ = increase or increased risk, ↓ = decrease or decreased risk, A77 1726 = active metabolite of leflunomide, AUC = area under the curve as a measure of bioavailability, Cmax = maximal plasma concentration, C5h = concentration at 5 hours after administration, MTX= methotrexate, Ref. = references.

Table 7. Assessment for immediate intervention per adverse reaction category.

Adverse reaction category	*Number of combinations in category*	*Requiring immediate intervention*		*P-value*
		Hospital pharmacists	*Rheumatologists*	
Increased toxicity DMARD	19	9	14	0.13
Decreased effectiveness DMARD	7	6	2	0.13
Increased toxicity non-DMARD	4	1	2	1.00
Decreased effectiveness non-DMARD	6	5	5	1.00
Other	4	1	1	1.00

Legend: DMARD = disease-modifying antirheumatic drug.

Considering the combinations for which both observer groups agreed on immediate intervention plus the combinations for which the observer groups disagreed, as combinations for which an alert from the CIS may be relevant, 27 of the 40 combinations remain. Each observer group has a sensitivity of 81% for these combinations, i.e. both groups identify 22 out of 27 combinations to require immediate intervention. Specificity for both groups is 81%, i.e. for 5 of the 27 combinations both observer groups would generate an alert or take immediate intervention where the other group would not require any immediate intervention.

Discussion

Our literature search yielded 40 potentially interacting drug combinations involving DMARDs within the predefined criteria. For 30 (75%) of these DDI rheumatologists and hospital pharmacists agreed regarding the requirement of an immediate intervention or not. Overall, rheumatologists tended to require immediate intervention more often for those combinations that increased the risk of toxicity of the DMARD, while hospital pharmacists more often required immediate intervention for combinations with an increased risk of ineffectiveness of the DMARD.

Of all possible drug combinations with DMARDs that could occur in clinical practice, for only 40 combinations information is found. A recent study concluded that for only 7.5% of

the total number of prescribed drug combinations in a general population participating in a health-screening program, information on the existence of a potential DDI was present [66]. When translating these results to the RA-population underreporting of potential clinically relevant DDI with DMARDs may be expected. Guidelines for research on potential DDI for newly registered drugs [67] may expand the knowledge on potential DDI. However, drugs on the market for several years often lack this information. This is reflected by the 43% of combinations in our study with evidence quality categorized as 0 to 2, and the lack of the highest level of evidence (grade 4) for any of the combinations.

Alerts generated by CIS have to be specific, sensitive and have to be accompanied by information for adequate management for the individual patient. In routine medical practice both physicians and pharmacists have the ability to respond to DDI alerts when using a CIS. In our study for 25 percent of the drug combinations the observer groups did not agree as to whether the combination required immediate intervention. Both observer groups especially diverged in their judgement whether or not immediate intervention is required based on the adverse reaction category. Due to these differences in perception of severity of the effect of a DDI, perceived specificity and sensitivity of the CIS may be suboptimal. Therefore, a multidisciplinary discussion as the basis for uptake of DDI in a CIS may increase clinical applicability of the alert generated by the CIS.

In our study ‘immediate intervention’ was broadly defined as any action to assure safe and effective use of the combination or to avoid the combination. Perception of the degree in which the DDI can be controlled, i.e. to what extent it may be possible to take action to prevent the adverse reaction, may be a source of differences in judgement between both observer groups. For example, when the combination shows an interaction based on decreased absorption from the gastrointestinal tract due to complexation (chloroquin/magnesiumtrisilicate, D-penicillamine/antacids, D-penicillamine/iron salts, D-penicillamine/digoxin, sulfasalazine/iron salts), the DDI can be controlled by spacing oral gifts of both medications by several hours. Hospital pharmacists judged that all these DDI should have required immediate intervention, while rheumatologists only judged immediate intervention required for 2 of these interactions. This stresses the differences in points of view between the observer groups and the necessity to assess the relevance of a combination through a multidisciplinary approach. Since approximately 75% of all DDI can be controlled [66], differences in opinion on the degree on which DDI can be controlled may introduce potential differences in assessment of requirement of immediate intervention for most DDI.

Some limitations of the current study need to be pointed out. Firstly, the differences between observer groups in our study may be specific for the field of rheumatology. Since, to our knowledge, no studies on this subject are published in other fields of medicine this has to be subject of study in the future. Secondly, no effort was made to reach consensus between both groups, implying that maximum contrast between observer groups is presented here. Despite these limitations our study is the first to provide valuable information on the differences in the assessment of the clinical relevance of DDI between two observer groups consisting of members from different specialties.

Conclusion

For 40 drug combinations including a DMARD clinical relevance was assessed by two observer groups, rheumatologists and hospital pharmacists. For a subset of 10 of these DMARD combinations rheumatologists and hospital pharmacists differed in the assessment of clinical relevance. Multidisciplinary judgement as the basis for uptake of DDI in a CIS may increase sensitivity and specificity, i.e. clinical applicability of the alerts generated by a CIS.

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Chapter 6

Summary, conclusions and future perspectives

Introduction

The field of rheumatology has changed in the past years. New treatment options are added to the pharmacotherapeutical armamentarium of the rheumatologist, outdated treatment options have disappeared. In this rapidly changing field the adequate implementation of new information for treatment of the individual patient is of great importance to obtain optimal treatment outcomes. From this point of view, the critical evaluation of outcomes in day-to-day care is obligatory to reach the goal of optimal therapy for every patient. This thesis studies different aspects of safety and efficacy of pharmacotherapy in the treatment of rheumatoid arthritis (RA). Studies in this thesis focus on leflunomide, parenteral gold and the clinical relevance of drug-drug interactions with disease-modifying antirheumatic drugs (DMARDs).

Leflunomide in daily clinical practice, options for treatment optimization

Summary and discussion

In **chapter 2** different studies concerning the treatment of rheumatoid arthritis with leflunomide in clinical rheumatological practice are described. In **chapter 2.1** we prospectively studied withdrawal from leflunomide, the incidence of adverse drug reactions and effectiveness of leflunomide in an outpatient population with RA. In this study 136 RA patients were included. We found that during follow-up 76 patients (56%) withdrew from leflunomide treatment, mainly because of adverse drug reactions (29%) or lack of effectiveness (13%). Sixty-five percent of patients experienced at least one adverse drug reaction related to leflunomide. Within a 12 month period after start of leflunomide treatment 76% of the evaluable patients were classified as moderate or good responder according to the disease activity counting 28 joints (DAS_{28}) response criteria. From the results of this study it was concluded that leflunomide offers an efficacious treatment option although the incidence of withdrawal from leflunomide therapy, mainly for the reason of adverse drug reactions, was high. The results of this study stress the importance of critical evaluative studies in the positioning of a novel DMARD in the setting of care-as-usual and demand optimization of the leflunomide treatment schedule and better recognition for patients at risk for treatment failure.

One of the adverse drug reactions of leflunomide which caught the attention was hepatotoxicity, mainly because of reports of several fatal events. Although rare, these events started the discussion on whether or not leflunomide had to be withdrawn from the market. Eventually, the discussion on hepatotoxicity led to adaptations in the product leaflet of leflunomide, with guidelines for close montoring of serum liver enzyme activities as marker for potential hepatotoxicity. Discussions on the safety of leflunomide following reports of rare, fatal hepatotoxic reactions are important in optimizing safe drug use. A critical evaluation of the magnitude of hepatotoxicity as detected trough clinical chemical testing in routine rheumatological practice is complementary to this discussion.

To gain insight in the timing, frequency and severity of elevated liver enzymes, a study on the incidence and severity of hepatotoxicity during leflunomide treatment in a cohort of RA patients in a setting of 'care-as-usual' is conducted. The results of this study are described in **chapter 2.2**. To categorize the severity of the liver enymze activities the Common Toxicity Criteria of the National Cancer Institute were used. According to these criteria elevated enzyme activities, compared with the activities regarded as the upper limit of normal activities, were categorized as moderate (grade 2), severe (grade 3) or life threatening (grade 4). In a population of 101 patients we found grade 2 or 3 elevations in any liver function blood test for 9 patients (8.9%). No grade 4 elevations and no clinical signs of serious hepatotoxicity were recorded. Due to grade 2 hepatotoxicity one patient (1%) was withdrawn from leflunomide treatment, and one patient continued leflunomide in a reduced dose. In eight of nine patients with grade 2-3 liver function blood tests, these elevated liver function tests occurred within 6 months after starting leflunomide. None of the patients with grade 2 or 3 toxicity had a history of hepatic disease, eight patients concomitantly used potential hepatotoxic co-medication. Eight (8%) patients used leflunomide in combination with methotrexate, one of these patients developed hepatotoxicity. From this study we concluded that, under conditions of continued monitoring of liver functions, hepatotoxicity during leflunomide use does not seem to be a major problem in our population.

As was concluded from the long-term observation described in **chapter 2.1**, early recognition of patients at risk for leflunomide treatment failure may be important for improvement in obtaining treatment goals. In **chapter 2.3** we describe the results of a study to determine predictors for leflunomide survival in an outpatient population with RA. A large dataset from two rheumatological practice in the regions of Friesland and Twente, was analysed to determine predictors for leflunomide survival. The dataset in this study consisted of 279 patients, of whom 173 patients (62,0%) withdrew from treatment during follow-up.

Univariate analysis showed concomitant systemic corticosteroid use and an erythrocyte sedimentation rate < 35 mm/hr at start of leflunomide to be predictive for better leflunomide survival. Furthermore, the attending rheumatologist was correlated with leflunomide drug survival. These variables were also found to be predictive for leflunomide survival in multivariate analysis. From this study we concluded that information on these predictors at the start of leflunomide therapy may offer opportunities for treatment optimization.

Following the high withdrawal rate from our observational study, ways for improving treatment outcomes were sought. One of the options in this context is the implementation of therapeutic drug monitoring: the determination of the serum concentrations of the active component of leflunomide as a means to adapt clinical practice when necessary.

In **chapter 3** the potential role for therapeutic drug monitoring in leflunomide therapy is studied. In **chapter 3.1** a high-performance liquid chromatography method with ultraviolet detection (HPLC-UV) was technically and clinically validated, to obtain a method for determination of A77 1726, the active metabolite of leflunomide. The method showed acceptable performance on all major aspects of the validation (linearity, intra- and inter-day precision, accuracy, specificity and lower/upper limits of quantitation). For clinical validation the serum A77 1726 concentrations in 37 RA patients on leflunomide therapy were determined using this HPLC-UV method. Measured serum A77 1726 serum concentrations in patient samples showed large variability with a range of 3 to 176 mg/L, with >95% of samples yielding A77 1726 serum concentrations within the validated range of the analytical method. From these results we concluded that the proposed method could be employed for the assay of A77 1726 in RA patient samples.

Using this assay we studied the relationship between A77 1726 steady state serum concentrations and DAS_{28}, respectively DAS_{28} response. The results of this study are described in **chapter 3.2**. For this study, fifty-two outpatients with RA on a stable leflunomide dose > 4 months were included. We concluded that A77 1726 steady state serum concentrations show a relationship with DAS_{28} response. More precisely, patients with A77 1726 serum concentrations < 16 mg/L did not show good response according to DAS_{28} criteria. This opens the option of determination of A77 1726 serum concentrations for patients with insufficient response to therapy, to gain clinically relevant information for decisions on treatment continuation or dose adjustment.

Future perspectives

From the first three studies in these chapters the main results are the high withdrawal rate within the first year after start of leflunomide treatment and the high percentage of patients experiencing adverse drug reactions, with hepatotoxicity being manageable under conditions of strict monitoring. This leads to the conclusion that further optimization of leflunomide therapy is warranted, to obtain the expected treatment outcomes.

Recognition of characteristics predictive for treatment failure may seem a rather basal strategy to obtain improvement in treatment outcomes. However, whether knowledge of the presence of a predictive factor for leflunomide survival in an individual patient will indeed lead to improvement in treatment outcomes, has to be the subject of future, prospective studies. One major factor in these future analyses will be the way in which this information is used in clinical practice. Do patients at higher risk of leflunomide withdrawal have to visit their rheumatologist more often compared with patients without an increased risk? And, when this is an option, what kind of information is collected during these visits to indeed improve clinical outcomes? Do patients at higher risk of withdrawal need to be treated with adapted dosing schedules, for example by leaving the loading dose or therapy maintenance with lower or higher daily doses than recommended in the product leaflets? These and other questions have to be answered to implement the predictive factors for therapy survival in daily rheumatological decision making.

One possibility for leflunomide treatment optimization is studied in the chapter concerning therapeutic drug monitoring. As stated in the discussion of this chapter, it would be interesting to know whether early decisions on therapy withdrawal or continuation are improved when decisions can be based on the combination of insufficient response and a low A77 1726 steady-state serum concentration. Under the assumption of therapy compliance and stable dosing, a direct relationship between duration of therapy, A77 1726 serum concentration at that moment and the A77 1726 steady state serum concentration exists. This leads to the hypothesis that a non-steady state A77 1726 serum concentration determined early in leflunomide therapy, for example after 4 weeks of treatment, may well predict patients response to therapy later on. Applying this hypothesis to leflunomide therapy, theoretically, offers the opportunity to make early decisions based on non-steady state A77 1726 serum concentrations and may prevent delay before therapy is switched to more efficacious alternatives for the individual patient. To what extent this approach will lead to improvements in leflunomide treatment outcomes has to be subject of further studies.

Confirmation of the results from our 'therapeutic drug monitoring' study in a larger, prospective study with patients on *de novo* leflunomide therapy is the proposed first step for future studies. Secondly, randomized studies comparing *de novo* leflunomide patients with RA, with and without information on the A77 1726 serum concentrations, have to be conducted. In these studies attention has to be given to the clinical decisions to be made when insufficient response, with or without information on the A77 1726 serum concentration, is encountered by patient and rheumatologist.

Switching parenteral gold preparations

Summary and discussion

After withdrawal of aurothioglucose from the Dutch market aurothiomalate was presented as the alternative preparation. Considering the active component of aurothiomalate, gold, this is not a remarkable choice for an alternative preparation. However, from the point of view of evidence based medicine, this view was remarkable, since no large studies for patients switching between both treatments were published.

Therefore, at the moment that aurothioglucose was withdrawn from the market a critical evaluation of the outcomes of gold therapy after switching from aurothioglucose to aurothiomalate was conducted. In this study, described in **chapter 4.1**, we followed a cohort of patients during the first year after switching from aurothioglucose to aurothiomalate to study effectiveness and safety. A total of 120 patients were included, from whom 19 patients (16%) reported an adverse drug reaction on aurothiomalate, not previously experienced on aurothioglucose. Twenty-nine patients (24%) patients withdrew from aurothiomalate within 12 months follow-up for reasons of ineffectiveness (14%), adverse drug reactions (7%) or disease in state of remission (3%). No statistically significant differences between the disease activity parameters during follow-up visits compared with the baseline visit were detected for the patients remaining on aurothiomalate. When comparing our data on withdrawal from aurothiomalate with data from other studies, we concluded that the withdrawal rate was lower compared with patients starting gold therapy *de novo*, but higher compared with patients on gold therapy for several years. The higher withdrawal rate and reports of novel adverse drug reactions, i.e. adverse drug reactions not previously reported on aurothioglucose treatment, suggest the introduction of a treatment with different characteristics compared with aurothioglucose. On the other hand we concluded from these

data that it is remarkable that only 24% of patients withdraw from aurothiomalate therapy in our study despite the occurrence of novel adverse drug reactions in some patients. A certain degree of satisfaction with current gold therapy may have played an important role in deciding to continue parenteral gold therapy.

Future perspectives

The results from this study learn us that critical evaluation of outcomes when choosing alternative treatments in case of withdrawal from already installed therapy, may provide insight in pitfalls in effectiveness or safety of the new treatment.

Clinical relevance of drug-drug interactions

Summary and discussion

In our studies in the field of drug-drug interactions we defined the goal of generating drug interaction alerts as ‘timely recognition of the opportunity to intervene in drug use in order to prevent an undesired effect as a result of a combination of drugs’. This definition clearly states that a drug interaction alert is useful only when an intervention is necessary and possible, for example prescribing and/or dispensing an alternative drug, dosage adjustment or adjusted monitoring of drug effects.

In an ideal situation the information necessary to take the appropriate actions is present at the moment of registration of the new drug, in scientific publications. However, this situation rarely exists. In most instances information on drug-drug interactions in product leaflets is too comprehensive to be of practical use and specific drug-drug interaction studies are absent. With the introduction of legislative guidelines concerning obligatory studies on the field of drug-drug interactions as part of the registration files, this situation may be improved.

Despite this improvement, the correct interpretation of the potential severity of an adverse effect resulting from a drug-drug interaction for the individual patient will remain a responsibility for health care providers. To fullfill this responsibility health care providers have to be informed, clearly and completely, on the relevant factors for making this interpretation.

In this context, electronic drug interaction surveillance systems can fullfill an important role, complementary to the informing and alerting function of the product leaflets. In **chapter**

5.1 a structured procedure for assessing the clinical relevance of a drug-drug interaction based on the evaluation of four core parameters is described. This procedure is developed and implemented by the Working Group on Pharmacotherapy and Drug Information in the maintenance of the electronic drug interaction surveillance system of the Royal Dutch Association for the Advancement of Pharmacy. On the basis of this assessment the complete database is reviewed resulting in 36% of the interacting combinations to be assessed as 'not interacting' or 'interacting but not requiring any action'. On the basis of experience with this procedure in the last few years, we concluded that this procedure offers the possibility for transparent and reproducible assessment of the clinical relevance of potential interacting drug combinations.

This assessment procedure is used for assessing the clinical relevance of drug-drug interactions with disease-modifying antirheumatic drugs. Results of this study are described in **chapter 5.2**. Two observer groups, rheumatologists and pharmacologists, independently assessed whether the individual combinations interacted and whether the combination required immediate intervention. From a total of 40 DMARD-drug combinations, 17 (43%) were judged to be interacting and require immediate intervention, 13 (32%) were judged not to require immediate intervention and for 10 combinations (25%) pharmacists and rheumatologists did not agree. Rheumatologists tended to require immediate intervention more often for drug-drug interactions with increased toxicity of the DMARD as the adverse reaction, while pharmacologists more often judged drug-drug interactions with an increased risk of DMARD failure to require immediate intervention. We conclude that due to differences in perception of severity of the effect of a DMARD-drug interaction, perceived specificity (generating an alert only when relevant) and sensitivity (generating an alert whenever relevant) of alerts generated by electronic drug interaction surveillance systems may be suboptimal when no multidisciplinary discussion is used for selection of drug-drug interactions.

Future perspectives

A structural assessment of potential drug interactions for selection for electronic drug interaction surveillance systems, can be considered to be a starting point for further research. It is to be expected that electronic interaction surveillance systems yielding alerts with high specificity and high sensitivity, as a result of multidisciplinary discussion, will support clinical decision making better, compared with systems with low specificity and sensitivity. However, this has to be subject of future studies. These studies, for example,

could focus on the acceptance of alerts from these systems by physicians and pharmacists. How often are alerts overruled without taking notice? How often is clinical decision making influenced due to an interaction alert? On the other hand, these studies could focus on the impact of the system on the quality of care, eventually with pharmacoeconomic analyses of the interventions.

Chapter 7

Samenvatting

Inleiding

Het werkterrein van de reumatologie is de laatste jaren door het beschikbaar komen van nieuwe behandelopties sterk veranderd. In dit snel veranderende veld is het van groot belang nieuwe informatie adequaat te implementeren en kritisch te evalueren om optimale behandeluitkomsten voor de individuele patiënt te realiseren.

Dit proefschrift bestudeert diverse aspecten van veiligheid en effectiviteit van farmacotherapie bij de behandeling van reumatoïde artritis (RA). De onderzoeken in dit proefschrift richten zich op leflunomide, parenteraal goud en de klinische relevantie van geneesmiddel-geneesmiddel interacties met de zogenaamde 'disease-modifying antirheumatic drugs' (DMARDs).

Leflunomide in de reumatologische praktijk

Samenvatting en discussie

In hoofdstuk 2 worden onderzoeken betreffende de behandeling van RA met leflunomide in de dagelijkse reumatologische praktijk beschreven. In **hoofdstuk 2.1** wordt prospectief het staken van de behandeling met leflunomide, het optreden van bijwerkingen en de effectiviteit van leflunomide onderzocht in een poliklinische populatie patiënten met RA. In dit onderzoek zijn 136 patiënten geïncludeerd. Tijdens de observatieperiode stopten 76 patiënten (56%) met leflunomide, met name in verband met het optreden van bijwerkingen (29%) of het ontbreken van (voldoende) effectiviteit (13%). Vijfenzestig procent van de patiënten meldde tijdens de observatieperiode minimaal 1 bijwerking die werd gerelateerd aan het gebruik van leflunomide. Binnen een periode van 12 maanden na start van de leflunomidebehandeling kon 76% van de populatie geclassificeerd worden als 'moderate' of 'good' responder, op basis van de ziekteactiviteit beoordeeld aan de hand van 28 gewrichten (disease activity score 28; DAS_{28}). Naar aanleiding van de resultaten van dit onderzoek werd geconcludeerd dat leflunomide een effectieve behandeling voor RA biedt, maar dat de kans op staken van de leflunomidebehandeling, met name door het optreden van bijwerkingen, hoog is. De resultaten van het onderzoek benadrukken het belang van kritisch evaluerende, observationele onderzoeken ter bepaling van de plaats van nieuwe DMARD-behandelopties in de dagelijkse reumatologische praktijk. Daarnaast wijzen de resultaten op de noodzaak om de behandeling met leflunomide te optimaliseren en te

komen tot een betere herkenning van patiënten die een groter risico hebben op therapeutisch falen.

Een van de bijwerkingen van leflunomide die veel aandacht heeft gekregen in de medische literatuur en de lekenpers was hepatotoxiciteit, met name door het optreden van enkele fataal verlopen incidenten. Hoewel zeldzaam, hebben deze incidenten de aanzet gegeven tot een discussie over de wenselijkheid van het op de markt houden van leflunomide voor de behandeling van RA. Uiteindelijk heeft deze discussie geleid tot aanpassingen in de productinformatie van leflunomide betreffende een striktere controle van de leverenzymactiviteiten, als maatstaf voor leverfunctiestoornissen. Discussies over de veiligheid van leflunomide naar aanleiding van enkele ernstige gevallen van hepatotoxiciteit zijn van groot belang om veilig geneesmiddelgebruik te optimaliseren. Een kritische evaluatie van de frequentie en ernst van hepatotoxiciteit zoals vastgesteld door klinisch-chemische bepaling van leverenzymactiviteiten in de dagelijkse reumatologische praktijk zijn op deze discussies een aanvulling.

Om inzicht te verkrijgen in de frequentie, de ernst en het moment van optreden van verhoogde leverenzymactiviteiten, is een onderzoek in een populatie patiënten met RA gedurende leflunomidetherapie uitgevoerd. De resultaten van dit onderzoek zijn beschreven in **hoofdstuk 2.2**. Om de ernst van de hepatotoxiciteit te kunnen categoriseren worden stijgingen van de leverenzymactiviteiten volgens de Common Toxicity Criteria van het National Cancer Institute ingedeeld. De Common Toxicity Criteria maken gebruik van een indeling van de ernst van bijwerkingen in moderate (graad 2), ernstig (graad 3) of levensbedreigend (graad 4), afhankelijk van de mate van stijging ten opzichte van de bovenste grens van de referentiewaarden. In een populatie van 101 patiënten vertoonden 9 patiënten (8,9%) een graad 2 of graad 3 stijging van de leverenzymactiviteit. Graad 4 stijgingen en klinische verschijnselen van hepatotoxiciteit werden in de observatieperiode niet vastgesteld. In verband met graad 2 leverenzymstijgingen is 1 patiënt (1%) gestopt met de leflunomidebehandeling, bij 1 patiënt werd de dagdosering leflunomide verlaagd. In 8 van de 9 patiënten met een graad 2 of graad 3 stijging trad deze stijging binnen 6 maanden na start van de leflunomidebehandeling op. Geen van de patiënten met een graad 2 of graad 3 stijging had een voorgeschiedenis waarin sprake was van leverziekten. Acht van de negen patiënten gebruikten naast leflunomide ook andere medicatie waarvan bekend is dat leverfunctiestoornissen kunnen optreden. Acht patiënten (8%) gebruikten leflunomide in combinatie met methotrexaat, 1 van deze patiënten ontwikkelde leverfunctiestoornissen. Naar aanleiding van de resultaten van dit onderzoek werd geconcludeerd dat, onder de

voorwaarde van strikte controle van de leverfuncties, in onze populatie hepatotoxiciteit gedurende het gebruik van leflunomide geen groot probleem lijkt.

Zoals geconcludeerd is naar aanleiding van de resultaten van de langetermijnobservatie die in hoofdstuk 2.1 is beschreven, kan vroege herkenning van patiënten met een grote kans van falen van de leflunomidebehandeling een handvat bieden voor verdere verbetering in het behalen van de beoogde behandeldoelen. Het continueren van de leflunomidebehandeling kan als maat voor het slagen of falen van de behandeling gebruikt worden. In **hoofdstuk 2.3** wordt een onderzoek beschreven waarin voorspellende factoren voor het continueren van de leflunomidebehandeling worden gezocht. Als basis voor dit onderzoek is gebruik gemaakt van een databestand van patiënten met RA, die in de regio's Friesland en Twente poliklinisch door een reumatoloog met leflunomide werden behandeld. Het databestand bevatte 279 patiënten, van wie er 173 (62%) het gebruik van leflunomide tijdens de observatieperiode staakten. Uit univariate en multivariate analyse bleek dat het gelijktijdig gebruik van systemische corticosteroïden en een bezinkingssnelheid < 35 mm/uur bij start van de leflunomidebehandeling voorspellend waren voor een langere periode van continueren van de leflunomidebehandeling. Verder werd naar aanleiding van de univariate en de multivariate analyse vastgesteld dat er tussen de behandelende reumatologen verschillen in de duur van continueren van de leflunomidebehandeling bestonden. Naar aanleiding van de resultaten van dit onderzoek werd geconcludeerd dat er factoren zijn die een voorspellende waarde ten aanzien van het continueren van de leflunomidebehandeling hebben. Informatie over deze voorspellende factoren kan mogelijkheden bieden voor verdere optimalisatie van leflunomidebehandeling.

Op basis van de hoge frequentie waarmee patiënten de behandeling met leflunomide beëindigen, werd onderzoek gedaan naar een manier om de uitkomsten van de leflunomidebehandeling te verbeteren. Een van de opties was implementatie van zogenaamde 'therapeutic drug monitoring'; dat wil zeggen de bepaling van de concentraties van de werkzame stof in het bloed en het gebruiken van de uitkomsten van deze bepaling als handvat voor het aanpassen van het therapeutisch beleid.

In hoofdstuk 3 wordt de potentiële rol van ' therapeutic drug monitoring' bij behandeling met leflunomide onderzocht. In **hoofdstuk 3.1** wordt een bepalingsmethode technisch en klinisch gevalideerd om de serumconcentraties van de werkzame metaboliet van leflunomide, A77 1726, te kunnen bepalen. De bepalingsmethode voldeed op alle onderdelen van de technische validatie (lineariteit, intra- en interday precisie, juistheid,

specificiteit en de bovenste en onderste grenzen voor kwantificering van de concentratie) aan de gestelde voorwaarden. Voor de klinische validatie werden met behulp van deze bepalingsmethode de serumconcentraties van A77 1726 bepaald bij 37 RA patiënten die gedurende minimaal 4 maanden met leflunomide werden behandeld. De gemeten A77 1726 serumconcentraties vertoonden een grote variatie, met een spreiding van 3 tot 176 mg/liter. Van 95% van de patiënten viel de gemeten concentratie binnen het gevalideerde concentratiegebied van de bepalingsmethode. Op basis van deze resultaten wordt geconcludeerd dat de gevalideerde methode kan worden toegepast bij de bepaling van de A77 1726 serumconcentraties bij patiënten met RA die worden behandeld met leflunomide.

Met behulp van deze bepalingsmethode werd het verband tussen de A77 1726 serumconcentraties en de DAS_{28} en de DAS_{28}-respons onderzocht. De serumconcentraties werden bepaald op een moment tijdens de behandeling waarop de maximale, constante serumconcentratie bereikt is, de zogenaamde ‘steady state’ concentratie. De resultaten van dit onderzoek worden beschreven in **hoofdstuk 3.2**. In dit onderzoek werden 52 patiënten met RA en gedurende minimaal 4 maanden een stabiele dosering leflunomide geïncludeerd. Dit onderzoek toonde dat er een verband is tussen de A77 1726 steady state serumconcentratie en de respons op basis van de DAS_{28}-criteria; patiënten met een A77 1726 steady state serumconcentratie < 16 mg/L vertoonden geen goede respons op basis van de DAS_{28}-criteria. Deze resultaten wijzen op de mogelijkheid voor bepaling van de A77 1726 serumconcentratie voor die patiënten die onvoldoende respons vertonen op de leflunomidebehandeling om klinisch relevante informatie te verkrijgen voor het continueren van de behandeling of het aanpassen van de dosering.

Toekomstperspectieven

De belangrijkste resultaten van het eerste hoofdstuk zijn de hoge frequentie waarmee de leflunomidebehandeling in het eerste jaar na start van de behandeling wordt gestaakt en het grote percentage patiënten dat bijwerkingen meldt. Dit leidt tot de conclusie dat verdere optimalisatie van de leflunomidebehandeling is aangewezen om optimale behandeluitkomsten voor de individuele patiënt te realiseren.

Herkenning van karakteristieken die de kans op therapiefalen kunnen voorspellen, lijkt een basale strategie om behandeluitkomsten te verbeteren. Echter, of kennis van deze voorspellende factoren inderdaad kan leiden tot verbetering van de behandeluitkomsten voor de individuele patiënt, dient te worden onderzocht in toekomstige, prospectieve onderzoeken. Op welke wijze kennis van de voorspellende factoren kan worden toegepast

zal een belangrijke factor zijn in deze toekomstige onderzoeken. Dienen patiënten met een hoger risico op therapiefalen frequenter te worden gecontroleerd door hun reumatoloog? Zo ja, op basis van welke informatie, naast de kennis van de voorspellende factoren, kunnen de behandeluitkomsten dan worden verbeterd? Dienen patiënten met een hogere kans op therapiefalen te worden behandeld met een afwijkend behandelschema, bijvoorbeeld door het weglaten van de oplaaddosis of door hogere of lagere onderhoudsdoseringen dan momenteel worden geadviseerd in de bijsluiter? Deze en andere vragen dienen te worden beantwoord om de voorspellende factoren voor therapiefalen te kunnen implementeren in het therapeutisch beleid.

Een mogelijkheid voor optimalisatie van leflunomidebehandeling is onderzocht in het hoofdstuk aangaande ‘therapeutic drug monitoring’. Zoals al gesteld in de discussie bij dit hoofdstuk, zou het interessant zijn te weten of beslissingen over continueren of stoppen van de leflunomidebehandeling vroeg in de therapie, kunnen worden gebaseerd op de combinatie van onvoldoende respons en een lage A77 1726 serumconcentratie. Onder de aannames van therapietrouw en stabiele dosering, bestaat er een duidelijke relatie tussen de duur van de therapie, de A77 1726 serumconcentratie op dat moment en de te bereiken ‘steady state’ serumconcentratie. Dit leidt tot de hypothese dat een niet-steady state A77 1726 serumconcentratie die vroeg in de behandeling is bepaald, bijvoorbeeld na 4 weken behandeling, zou kunnen worden gebruikt ter voorspelling van de respons later in de therapie. Toepassing van deze hypothese zou kunnen leiden tot de mogelijkheid om vroeg in de behandeling beslissingen te nemen over het continueren, aanpassen of staken van de leflunomidebehandeling en daarmee vertraging te voorkomen voordat wordt overgestapt op effectievere alternatieve behandelingen voor de individuele patiënt. In welke mate deze benadering zal leiden tot verbeterde uitkomsten van de behandeling zal onderwerp dienen te zijn van verder onderzoek.

Bevestiging van de resultaten van ons ‘therapeutic drug monitoring’ onderzoek in een groter, prospectief onderzoek met patiënten op *de novo* leflunomidetherapie is de voorgestelde eerste stap voor toekomstig onderzoek. De tweede stap kan bestaan uit een gerandomiseerd onderzoek waarin uitkomsten van *de novo* leflunomidebehandeling bij RA patiënten, met of zonder informatie over de A77 1726 serumconcentraties, worden vergeleken.

Wisselen van preparaten voor parenterale toediening van goudzouten

Samenvatting en discussie

Na het terugtrekken van aurothioglucose (Auromyose®) van de Nederlandse markt werd aurothiomalaat (Tauredon®) als alternatief preparaat geadviseerd. Op basis van de actieve component van Auromyose® en Tauredon®, goud, is deze keuze niet opvallend. Vanuit het oogpunt van 'evidence based medicine' is dit advies echter wel opvallend, daar geen grote vergelijkende onderzoeken tussen beide preparaten op het gebied van veiligheid en effectiviteit zijn gepubliceerd.

Om deze reden is een kritische evaluatie van de uitkomsten van aurothiomalaat behandeling, na wisselen van aurothioglucose, aangewezen. Onderzoek naar deze uitkomsten is beschreven in **hoofdstuk 4.1**. In dit onderzoek is een populatie patiënten gedurende het eerste jaar na wisselen van aurothioglucose- naar aurothiomalaatbehandeling gevolgd, om effectiviteit en veiligheid van de behandeling te bestuderen. De geïncludeerde populatie bestond uit 120 patiënten, waarvan er 19 (16%) een bijwerking meldden die niet eerder tijdens de behandeling met aurothioglucose was gemeld. Gedurende de 12 maanden durende observatieperiode staakten 29 patiënten (24%) het gebruik van aurothiomalaat in verband met onvoldoende effectiviteit (14%), bijwerkingen (7%) of ziekte in remissie (3%). Er werden geen statistische significante verschillen gevonden in de parameters voor ziekteactiviteit ten opzichte van deze parameters bij start van de aurothiomalaatbehandeling voor die patiënten die de behandeling continueerden gedurende 12 maanden. Uit vergelijking van de frequentie van staken van aurothiomalaat in ons onderzoek en andere onderzoeken, blijkt dat de in dit onderzoek gevonden frequentie van staken lager is dan bij patiënten die *de novo* starten met parenterale goudbehandeling, maar hoger is dan bij patiënten op langdurige (jaren) goudtherapie. De hogere frequentie van therapiestaken en de meldingen van bijwerkingen die niet eerder gemeld zijn tijdens aurothioglucosebehandeling, suggereren dat met de behandeling met aurothiomalaat een behandeling is gestart met andere karakteristieken dan de aurothioglucosebehandeling. Dat slechts 24% van de patiënten het gebruik van aurothiomalaat binnen 12 maanden staakt, weerspiegelt mogelijk een zekere mate van tevredenheid met de huidige goudtherapie als basis voor beslissingen over continueren van de behandeling.

Toekomstperspectieven

De resultaten van dit onderzoek leren ons dat een kritische evaluatie van behandeluitkomsten bij het kiezen van alternatieve behandelingen in geval van het terugtrekken van een reeds gestarte behandeling, inzicht kan geven in effectiviteit en veiligheid van de nieuwe behandeling.

Klinische relevantie van geneesmiddel-geneesmiddel interacties

Samenvatting en discussie

In de onderzoeken op het gebied van geneesmiddelinteracties is het doel van het signaleren van een geneesmiddelinteracties gedefinieerd als ‘de tijdige herkenning van de mogelijkheid om te interveniëren in geneesmiddelgebruik met als doel te voorkomen dat een ongewenst effect ten gevolge van combinaties van geneesmiddelen optreedt.’ Deze definitie maakt duidelijk dat een geneesmiddelinteractiesignaal alleen bruikbaar is als een interventie mogelijk en nodig is, bijvoorbeeld door het voorschrijven van een alternatief geneesmiddel, het aanpassen van de dosering of een aanpassing in de monitoring van het geneesmiddeleffect. In de ideale situatie is alle informatie die nodig is om de vereiste interventie te plegen, aanwezig op het moment dat het nieuwe geneesmiddel geregistreerd wordt. Helaas is deze situatie slechts zelden realiteit. In de meeste gevallen is de informatie over geneesmiddel-geneesmiddelinteracties in de bijsluiter te beknopt om direct toe te passen in het klinische beslisproces en ontbreken gepubliceerde onderzoeken op het gebied van geneesmiddelinteracties. Met de introductie van regelgeving op het gebied van verplichte onderzoeken naar geneesmiddelinteracties als onderdeel van het registratiedossier kan deze situatie verbeteren.

Ondanks deze mogelijke verbetering, blijft de correcte interpretatie van de relevantie van de geneesmiddelinteractie voor de individuele patiënt de verantwoordelijkheid van de zorgverleners, met name artsen en apothekers. Om deze verantwoordelijkheid vorm te kunnen geven, dienen deze zorgverleners volledig en duidelijk te worden geïnformeerd over de kritische factoren betreffende de geneesmiddelinteractie om zich de juiste interpretatie te kunnen vormen.

Een elektronisch geneesmiddelinteractie begeleidingssysteem kan vanuit deze optiek een belangrijke rol vervullen, aanvullend aan de informatie in de bijsluiter. In **hoofdstuk 5.1** wordt een gestructureerde procedure beschreven voor de beoordeling van de relevantie van

geneesmiddel-geneesmiddel interacties gebaseerd op de evaluatie van vier kernparameters: de kwaliteit van de bewijslast, de ernst van het potentiële effect, risicofactoren voor het optreden van het effect en de incidentie van het effect ten gevolge van de interactie. Deze procedure is ontwikkeld door de Werkgroep Farmacotherapie en Geneesmiddelinformatie en in het onderhoud van het elektronisch geneesmiddelinteractie begeleidingssysteem van de Koninklijke Nederlandse Maatschappij ter bevordering van de Pharmacie (KNMP) geïmplementeerd. Op basis van de beoordeling volgens deze procedure is de gehele bestaande database herzien. Deze herziening heeft ertoe geleid dat 36% van de interagerende combinaties als ‘geen interactie’ of ‘interactie, maar geen interventie nodig’ is beoordeeld. Op basis van de ervaring met het gebruik van deze procedure in de afgelopen jaren wordt geconcludeerd dat deze procedure de mogelijkheid biedt voor transparante en reproduceerbare beoordeling van de klinische relevantie van potentieel interagerende geneesmiddelcombinaties.

Deze beoordelingssystematiek is voor bepaling van de klinische relevantie van geneesmiddel-geneesmiddel interactie met de DMARD’s gebruikt. De resultaten van dit onderzoek zijn beschreven in **hoofdstuk 5.2**. Twee groepen beoordelaars, reumatologen en farmacologen, beoordeelden onafhankelijk of er bij de individuele geneesmiddelcombinaties sprake was van een interactie en of deze interactie vervolgens een interventie vereiste. Van het totaal van 40 geselecteerde geneesmiddelcombinaties werden er 17 (43%) beoordeeld als interacties die een interventie vereisten, 13 (32%) als combinaties die geen interventie vereisten en voor 10 (25%) combinaties kwamen de beide beoordelaarsgroepen niet tot hetzelfde oordeel. Het onderzoek liet een trend zien waarbij reumatologen vaker dan farmacologen een interventie relevant achtten voor combinaties waarbij het effect een verhoogde kans op bijwerkingen van het DMARD betrof. Farmacologen bleken een interventie eerder relevant te achten voor die combinaties waarbij het potentiële effect een verminderde effectiviteit van het DMARD betrof. Op basis van deze resultaten wordt geconcludeerd dat door verschillen in de beoordeling van de relevantie van geneesmiddelinteracties, de beleving van specificiteit (alleen een interactiesignaal genereren indien vereist) en sensitiviteit (in alle vereiste gevallen een signaal genereren) van signalen die door elektronisch geneesmiddelinteractie begeleidingssystemen worden gegenereerd als suboptimaal worden ervaren, indien deze systemen niet worden gevoed met combinaties die zijn geselecteerd op basis van multidisciplinaire discussie.

Toekomstperspectieven

Van een elektronisch geneesmiddelinteractie begeleidingssysteem dat signalen genereert met hoge specificiteit en sensitiviteit op basis van multidisciplinaire beoordeling, mag een betere ondersteuning van het klinisch beslisproces worden verwacht dan van een systeem met lagere specificiteit en sensitiviteit. Of deze verwachting ook bewaarheid wordt en of betere behandeluitkomsten worden gerealiseerd, dient te worden onderzocht in toekomstig onderzoek. Dit onderzoek kan zich op de acceptatie van interactiesignalen door artsen en apothekers richten. Hoe vaak en om welke redenen worden interactiesignalen genegeerd zonder adequate interventie? Hoe vaak wordt het klinisch beslisproces door een interactiesignaal beïnvloed? En welke invloed heeft dit alles op de kwaliteit van zorg voor de individuele patiënt?

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een snelle printer. De inkt is eigenlijk nog niet droog, maar de correcties en aanpassingen staan er al bij. Ik denk met plezier terug aan de avonden waarop we met een goed glas rode wijn boomden over lopende en toekomstige onderzoeken. Wat mij betreft zetten we dat in de toekomst onverminderd voort. Bedankt voor je inspanning om dit proefschrift te maken tot wat het is geworden.

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